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### (54) Alpha-arylethylpiperazine derivatives as neurokinin antagonists

(57) The invention relates to new  $\alpha$ -arylethylpiperazine derivatives, which are useful as neurokinin receptor antagonists (NK<sub>1</sub>antagonists). It also relates to processes for the preparation of said  $\alpha$ -arylethylpiperazine de-

rivatives, to their use for the prevention and/or treatment of a condition associated with pathological levels of substance P in a patient and to pharmaceutical compositions containing them.

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**Description**

**[0001]** The present invention relates to new  $\alpha$ -arylethylpiperazine derivatives, which are useful as neurokinin receptor antagonists (NK<sub>1</sub> antagonists). It also relates to processes for the preparation of said  $\alpha$ -arylethylpiperazine derivatives, to their use for the prevention and/or treatment of a condition associated with pathological levels of substance P in a patient and to pharmaceutical compositions containing them.

**[0002]** Neurokinins (also called NKs or tachykinins) are a family of small peptides which are released from neuronal sensory afferents and which share a common carboxy-terminal region Phe-X-Gly-Leu-Met-NH<sub>2</sub>; in mammals, the main members are substance P (SP), neurokinin A (NKA, also known as substance K) and neurokinin B (NKB, also known as neuromedin K), which act as neurotransmitters and neuromodulators (C.A. Maggi, R. Patacchini, P. Rovero, A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93). These three types of neurokinins possess different degrees of potency; their endogenous agonist effect occurs via specific receptors. Three types of neurokinin receptors have been identified: NK<sub>1</sub> (SP-preferring), NK<sub>2</sub> (NKA-preferring) and NK<sub>3</sub> (NKB-preferring), which are widely distributed throughout the central nervous system (CNS) and peripheral nervous system (E. Burcher, C.J. Mussap, J.A. Stephenson, *Tachykinin Receptors*, Ed. Buck SH, Humana Press, Totowa, N.J. (1994), 125-163; J.E. Maggio, P.W. Mantyh, L.L. Iversen, *ibid*, 1-38).

**[0003]** Neurokinins have been described to be implicated in numerous physiological and pathological processes such as neuronal modulation, plasma protein extravasation, mast cell degranulation and mitogenic effects (C.A. Maggi, R. Patacchini, P. Rovero, A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93). In the peripheral nervous system, evidence suggests that neurokinins released from peripheral endings of sensory nerves are responsible for the phenomenon of neurogenic inflammation. Within the CNS, SP may serve as a neuromodulator of inputs from unmyelinated C-fibers involved in nociception to the central terminals of primary sensory neurones in the brainstem and spinal cord dorsal horn, suggesting a clinical utility for NK<sub>1</sub> receptor antagonists in the treatment of pain, particularly migraine (S. M. Moussaoui et al., *Eur. J. Pharmacol.* (1993) 238, 421-4; F.M. Curtler et al., *Neuroscience* (1995) 64, 741-50). SP-containing afferent nerve fibers also innervate the brain region of the nucleus tractus solitarius, an area involved in the control of emesis, suggesting the use of NK<sub>1</sub> receptor antagonists as antiemetics (F.D. Tattersall, W. Rycroft, R.G. Hill, R.J. Hargreaves, *Neuropharmacology* (1994) 33, 259-60; J.W. Watson, S.F. Gonsalves, A.A. Fossa et al., *Br. J. Pharmacol.* (1995) 115, 84-94). In the lung, neurokinins are released as a consequence of inflammatory processes and cause plasma protein extravasation, oedema formation, increased blood flow and mucus hypersecretion via NK<sub>1</sub> receptors (J.A. Lowe, *Emerging Drugs* (1996) 1-18). Thus selective NK<sub>1</sub> antagonists may have a potential therapeutic indication in the treatment of pulmonary diseases, in particular asthma and bronchitis.

**[0004]** There is also evidence supporting a role for SP in allergic rhinitis. First, in patients with allergic rhinitis, nasal SP content significantly increases immediately after nasal allergen challenge. Moreover, at the clinical peak of the late allergic reaction, SP levels are also raised (B.L. Mosimann et al., *J. Allergy Clin. Immunol.* (1993) 92, 95-104). Second, in allergic rhinitis, intranasal SP challenges induce vasodilatation, plasma leakage and recruitment of inflammatory cells (I. Fajac et al., *Allergy* (1995) 50, 970-5; A. Konn et al., *Ann. Otol. Rhino. Laryngol.* (1996) 105, 648-53) and the reduction of SP content in nasal secretions (after chronic capsaicin treatment) is related to the reduction of the clinical symptoms of allergic rhinitis (R. Zhang et al., *Chung Hua Erh Pi Yen Hou Ko Tsa Chih* (1995) 30, 163-5). Third, SP enhances antigen-evoked mediator release from human nasal mucosa by interaction with mast cells (C.R. Baumgarten C.R. et al., *Peptides* (1996) 17, 25-30).

**[0005]** The first potent non-peptide NK<sub>1</sub> receptor antagonists, i.e. CP-96,345 (R.M. Snider, S.J.W. Constantine, J.A. Lowe et al. *Science* (1991) 251, 435-7) and RP-67,580 (J.F. Peyronel, A. Truchon, C. Moutonnier, C. Garret, *Bioorg. & Med. Chem. Lett.* (1992) 2, 37-40) were discovered in 1991-1992. While CP-96,345 exhibited good selectivity for NK<sub>1</sub> receptors with respect to NK<sub>2</sub> and NK<sub>3</sub> receptors, it showed significant affinity for a number of ion channels, notably the verapamil-sensitive L-type Ca<sup>2+</sup> binding site (M. Caeser, G.R. Seabrook, J.A. Kemp, *Br. J. Pharmacol.* (1993) 109, 918-24). Such properties are undesirable from a therapeutic point of view because they are indicative of potential cardiovascular side-effects. This finding led to the discontinuation of further preclinical and clinical investigation of the compounds. Structure-activity relationship (SAR) modifications based on CP-96,345 provided other clinical candidates. For example CP-99,994 was determined to have good NK<sub>1</sub> selectivity and lower interaction with the verapamil-sensitive L-type Ca<sup>2+</sup> binding site than CP-96,345 (T. Rosen, T.F. Seegar, S. McLean et al., *J. Med. Chem.* (1993) 36, 3197-3201). It was evaluated in phase II clinical trials for asthma but first trials were reported unsuccessful, possibly due to its poor bioavailability (J.A. Lowe, *Emerging Drugs* (1996) 1-18 ; J.V. Fahy, H.F. Wong, P. Gepetti et al., *Am. J. Respir. Crit. Care Med.* (1995) 152, 879-884).

**[0006]** As to RP-67,580, it exhibited some NK<sub>1</sub> affinity. Molecular modifications by SAR led to improved candidates, such as RP-100,893, for example. It has been evaluated in clinical trials for the treatment of migraine; however, activity after oral administration was reported to be no better than placebo activity, possibly due to poor brain penetration (C. J. Swain, R.J. Hargraves, *Annual Reports in Medicinal Chemistry*, Vol. 31, Bristol, J.A. (Ed.) Academic Press: San Diego (1996) 111-120).

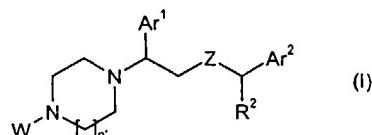
[0007] In view of the undesirable side-properties of these first non-peptide neurokinin antagonists, intensive work has been carried out by various teams in order to find other non-peptide NK<sub>1</sub> antagonists.

[0008] In particular, patent application WO 94/14767 and patent US 5624947 disclose aromatic compounds presented as valuable in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinins, in particular substance P, one of these compounds being the hydrochloride salt of ( $\pm$ )-1-[3,5-bistrifluoromethylphenyl)methoxy]-2-N-morpholino-2-phenylethane. Patent application DE 19520499 discloses disubstituted piperazines and piperidines presented for their neurokinin receptor antagonist properties. Amongst the most promising candidates, this document discloses 3,5-bistrifluoromethylbenzyl-[2-(2-methoxyphenyl)-2-(4-(2-phenylethyl)-piperazin-1-yl)-ethyl]-amine, 3,5-bistrifluoromethylbenzyl-[2-(2-methoxyphenyl)-2-(4-cycloheptylpiperazin-1-yl)-ethyl]-amine and 3,5-bistrifluoromethylbenzyl-[2-(2-methoxyphenyl)-2-(4piperidin-1-yl)-piperidin-1-yl]-ethyl]-amine.

[0009] We have now found other non-peptide selective NK<sub>1</sub> receptor antagonists with no or low affinity for Ca<sup>2+</sup> ion channels and which exhibit good oral bioavailability and duration of action, these compounds exhibiting useful properties for the prevention and/or treatment of a condition associated with pathological levels of substance P in a patient.

[0010] Accordingly, the present invention relates to new  $\alpha$ -arylethylpiperazine derivatives of formula I

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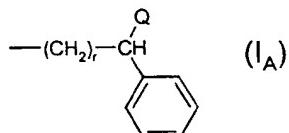
25 wherein

- Z represents O or S;
- n' represents 1 or 2;
- R<sup>2</sup> represents a hydrogen atom or a methyl group;
- W represents

30

- (i) a cyclohexyl group substituted by a COOH, 2-phenylacetic acid or alkyl 2-phenylacetate group,
- (ii) a group of formula

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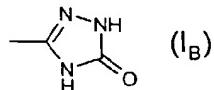
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- wherein r represents 1, 2 or 3 and Q represents OH or -NH-CO-CH<sub>3</sub>, or
- (iii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which

45

- R<sup>1</sup> represents a CN, CONR<sup>i</sup>R<sup>ii</sup>, CONHOH, CONHCH<sub>2</sub>CO<sub>2</sub>H, CONHCH<sub>2</sub>CO<sub>2</sub>alkyl, CONHSO<sub>2</sub>alkyl, CONHSO<sub>2</sub>phenyl, CONHSO<sub>2</sub>tolyl, COOH, COOalkyl, OH, SO<sub>3</sub>H, PO(OR<sup>iii</sup>)(OR<sup>iv</sup>) group, a mono-, di- or tri- substituted phenyl group in which the substituent is selected from COOH, COOalkyl or OCH<sub>3</sub>, a heteroaryl, a tetrazole, a morpholine, a thiomorpholine, a thiomorpholine S,S-dioxide, a phthalimide group or a triazolone of formula

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wherein R<sup>i</sup>, R<sup>ii</sup>, R<sup>iii</sup> and R<sup>iv</sup> independently represent a hydrogen atom or an alkyl group;

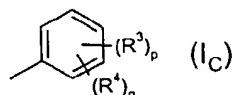
- X represents a single bond, an oxygen atom or a methylene group;
- m represents 1 or 2, provided that m is not 1 when X is O;
- n represents 0, 1 or 2, provided that N is not 0 or 1 when X represents O and R<sup>1</sup> represents OH;
- Ar<sup>1</sup> represents a phenyl, aryl, heteroaryl, or mono-, di- or tri-substituted phenyl group in which the substituents are

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selected from a halogen atom, an alkyl, trifluoromethyl, hydroxy, alkoxy,  $\text{SCH}_3$ , CN,  $\text{NO}_2$ ,  $\text{CONH}_2$ , COOH,  $\text{COOalkyl}$  or amino group, or mono-substituted heteroaryl group in which substituent is a halogen atom;

- $\text{Ar}^2$  represents a substituted phenyl group of formula

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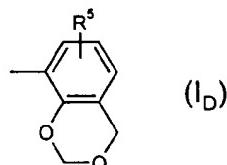


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in which

- $\text{R}^3$  represents a halogen atom, an alkyl, alkoxy, trifluoromethyl, COOH, CN,  $\text{COOalkyl}$  or  $\text{CONH}_2$  group;
- $\text{R}^4$  represents a halogen atom, a trifluoromethyl or alkyl group;
- p and q independently represent 0, 1, 2 or 3; or a group of formula

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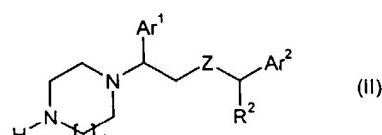


20 in which  $\text{R}^5$  represents a halogen atom;

25 all alkyl and alkoxy groups being linear or branched and having from 1 to 4 atoms of carbon, as well as non-toxic pharmaceutically acceptable salts, individual optical isomers, individual diastereoisomers or pro-drugs thereof.

[0011] The present invention also relates to new  $\alpha$ -arylethylpiperazine derivatives of formula II

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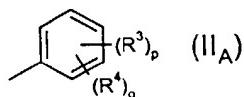


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wherein

- Z represents O or S;
- n' represents 1 or 2;
- $\text{R}^2$  represents a hydrogen atom or a methyl group;
- $\text{Ar}^1$  represents a phenyl, aryl, heteroaryl, or mono-, di- or tri-substituted phenyl group in which the substituents are selected from a halogen atom, an alkyl, trifluoromethyl, hydroxy, alkoxy,  $\text{SCH}_3$ , CN,  $\text{NO}_2$ ,  $\text{CONH}_2$ , COOH,  $\text{COOalkyl}$  or amino group, or a mono-substituted heteroaryl group in which substituent is a halogen atom;
- $\text{Ar}^2$  represents a substituted phenyl group of formula

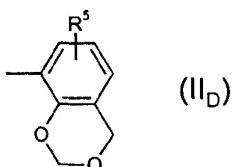
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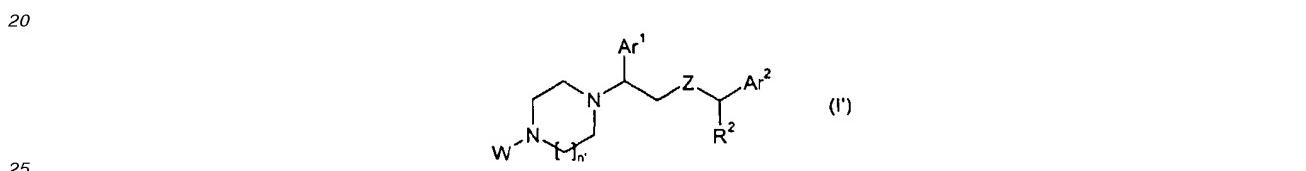
in which

- $\text{R}^3$  represents a halogen atom, an alkyl, alkoxy, trifluoromethyl, COOH, CN,  $\text{COOalkyl}$  or  $\text{CONH}_2$  group;
- $\text{R}^4$  represents a halogen atom, a trifluoromethyl or alkyl group;
- p and q independently represent 0, 1, 2 or 3, provided that p is not 0 and q is not 0 when  $\text{Ar}^1$  is a phenyl para-substituted by a fluorine atom;

or a group of formula

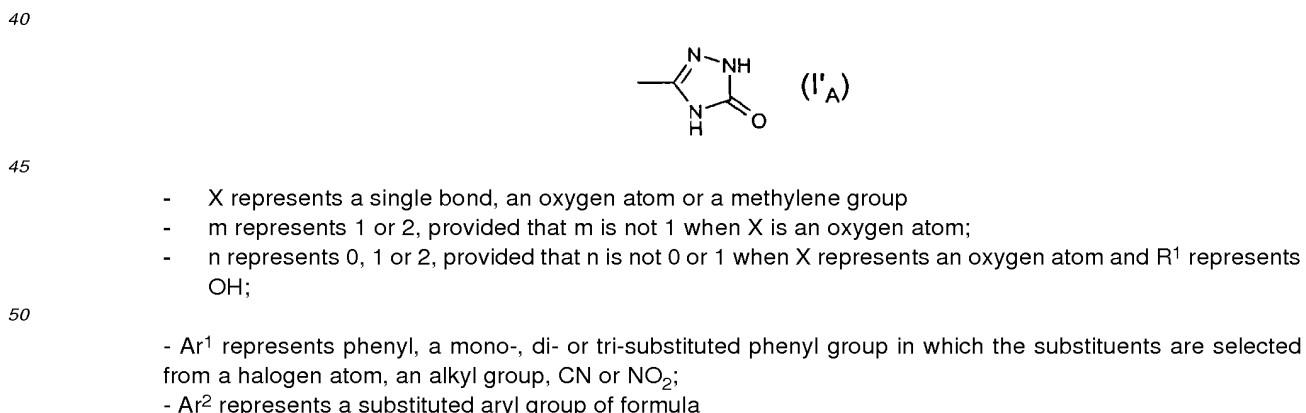


- 10 in which R<sup>5</sup> represents a halogen atom;  
 all alkyl and alkoxy groups being linear or branched and having 1 to 4 atoms of carbon;  
 as well as non-toxic pharmaceutically acceptable salts, individual optical isomers or individual diastereoisomers thereof.  
 [0012] The expression halogen atom as used herein includes fluorine, chlorine, bromine and iodine atoms.  
 15 [0013] The expression aryl as used herein includes 1-naphthyl or 2-naphthyl groups.  
 [0014] The expression heteroaryl as used herein includes pyridine, quinoline, isoquinoline, furan, thiophen, benzofuran, benzothiophuran or indole.  
 [0015] Preferred compounds according to the present invention are  $\alpha$ -arylethylpiperazine derivatives of formula I'



wherein

- 30 - Z represents an oxygen atom;  
 - n' represents 1;  
 - R<sup>2</sup> represents a hydrogen atom or a methyl group;  
 - W represents  
 (i) a cyclohexyl group substituted by COOH, or  
 (ii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which  
 - R<sup>1</sup> represents CN, CONHSO<sub>2</sub>alkyl, COOH, COOalkyl, SO<sub>3</sub>H, PO(OH)<sub>2</sub>, a phenyl group mono-substituted by COOH, a tetrazole group or a triazolone of formula



in which

- R<sup>3</sup> represents a halogen atom or a trifluoromethyl group;
- p represents 0, 1, 2 or 3;

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the alkyl groups being linear or branched and having 1 to 4 atoms of carbon, as well as non-toxic pharmaceutically acceptable salts, individual optical isomers, individual diastereoisomers or prodrugs thereof.

**[0016]** Particularly preferred compounds according to the invention include

- 10 - [2-(4-{2-(1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl}-piperazin-1-yl)-ethoxy]-acetic acid;
- (4-{2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl}-piperazin-1-yl)-acetic acid;
- 4-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-cyclohexanecarboxylic acid;
- 6-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-hexanoic acid;
- {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetonitrile;
- 15 - 3-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-propane-1-sulfonic acid;
- 5-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-pentanoic acid;
- (2-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetic acid;
- {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetic acid;
- {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-(3,4,5-trifluoro-phenyl)-ethyl]-piperazin-1-yl}-acetic acid;
- 20 - 4-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-ylmethyl}-benzoic acid;
- {4-[2-(3,5-Dibromo-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetic acid;
- {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-para-tolyl-ethyl]-piperazin-1-yl}-acetic acid;
- (2-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethyl)-phosphonic acid;
- {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-(2,3-difluoro-phenyl)-ethyl]-piperazin-1-yl}-acetic acid;
- 25 - {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-(2-nitro-phenyl)-ethyl]-piperazin-1-yl}-acetic acid;
- N-[(2-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-ethoxy}-acetyl)-methanesulfonamide;
- {4-[2-(3,5-Dichloro-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetic acid;
- {4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-(4-cyano-phenyl)-ethyl]-piperazin-1-yl}-acetic acid;
- 30 - 5-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-ylmethyl}-2,4-dihydro-[1,2,4]triazol-3-one;
- 1-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine;
- 1-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-4-[2-(1H-tetrazol-5-ylmethoxy)-ethyl]-piperazine;
- 1-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-(4-fluoro-phenyl)-ethyl]-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine;
- 1-[2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl]-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine;
- 35 - 1-[2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl]-4-[5-(1H-tetrazol-5-yl)-pentyl]-piperazine;
- (2-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetic acid isobutyl ester;
- 3-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-ylmethyl}-benzoic acid;
- 4-{4-[2-(3,5-Bis-trifluoromethyl-benzylxy)-1-phenyl-ethyl]-piperazin-1-yl}-butyric acid;

40 as well as non-toxic pharmaceutically acceptable salts, individual optical isomers or individual diastereoisomers thereof.

**[0017]** The present invention also relates to non-toxic pharmaceutically acceptable salts of  $\alpha$ -arylethylpiperazine derivatives of formula I. Such pharmaceutically acceptable salts include non-toxic pharmaceutically acceptable acid addition salts of  $\alpha$ -arylethylpiperazine derivatives of formula I. As examples there may be mentioned salts of mineral acids, such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acids and salts of organic acids, such as acetic, citric, tartaric, benzoic, salicylic and maleic acids. Anhydrous and hydrated forms of such salts are also encompassed by the present invention.

**[0018]** When the compound of formula I carries an acid moiety, pharmaceutically acceptable salts of compounds of formula I also include metal salts such as alkaline metal salts (such as sodium, potassium) or alkaline earth metal salts (such as calcium or magnesium salts).

**[0019]** When the molecule contains one or several asymmetric carbon atoms, the compound of formula I may either be in the form of a racemic mixture, in the form of one of its individual enantiomers or in the form of one of its individual diastereoisomers. It is to be understood that all such individual enantiomers and diastereoisomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

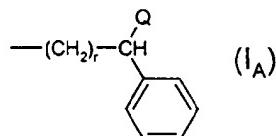
**[0020]** The term prodrugs as used herein refers to compounds which are rapidly transformed in vivo into the compounds of general formula I (see T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C. S. Symposium Series, and Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987 for a detailed discussion).

[0021] The  $\alpha$ -arylethylpiperazine derivatives of formula I may be prepared by one of the following processes:

5 (a) when, in formula I, Ar<sup>1</sup> represents a phenyl, aryl or heteroaryl group, a mono-, di- or trisubstituted phenyl group in which the substituents are selected from a halogen atom, an alkyl, trifluoromethyl, alkoxy, SCH<sub>3</sub> or NO<sub>2</sub> group, or a mono-substituted heteroaryl group in which substituent is a halogen atom, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' having the same meanings as given above in general formula I, and, furthermore,

10 (a.1) when, in formula I, W represents

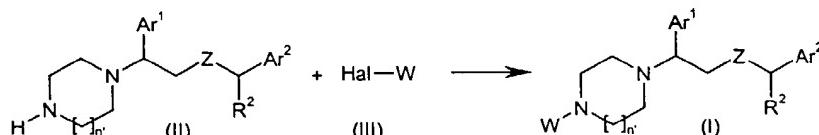
- (i) an alkyl 2-phenylacetate group,  
 (ii) a group of formula



20 wherein r represents 1, 2 or 3 and Q represents OH, or  
 (iii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which

25 R<sup>1</sup> represents a CN, CONR<sup>i</sup>R<sup>ii</sup>, COOalkyl, OH, SO<sub>3</sub>H or PO(OR<sup>iii</sup>)(OR<sup>iv</sup>) group, a mono-, di- or tri-substituted phenyl group in which the substituent is COOalkyl or OCH<sub>3</sub>, a pyridine, morpholine, thiomorpholine, thiomorpholine-(S,S)-dioxide or phthalimide group, wherein R<sup>i</sup> and R<sup>ii</sup> represent a hydrogen atom or an alkyl group and R<sup>iii</sup> and R<sup>iv</sup> represent an alkyl group,  
 n, m and X having the same meanings as given above in general formula I,

30 an  $\alpha$ -arylethylpiperazine of formula II is reacted with a compound of formula III according to the equation



40 wherein Ar<sup>1</sup>, Ar<sup>2</sup>, Z, R<sup>2</sup>, n' and W have the same meanings as stated above and Hal represents a halogen atom, preferably a chlorine, bromine or iodine atom.

45 This reaction is known per se and is generally carried out in an inert solvent, for example toluene, dimethylformamide, an alcohol or dichloroethane, in the presence of an acid acceptor, such as a tertiary organic base, for example triethylamine, or an inorganic base, for example sodium carbonate, sodium hydrogenocarbonate, potassium carbonate or potassium hydrogenocarbonate.

(a.2) when, in formula I, W represents

- 50 (i) 2-phenylacetic acid, or  
 (ii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which

55 R<sup>1</sup> represents CONHCH<sub>2</sub>CO<sub>2</sub>H, COOH, PO(OH)(OEt), PO(OH)<sub>2</sub> or a mono-, di- or trisubstituted phenyl group in which the substituents are COOH,

n, m and X having the same meanings as given above in general formula I,  
 the corresponding compound of formula I wherein W is

- 55 (i) an alkyl 2-phenylacetate or  
 (ii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which R<sup>1</sup> represents CN, CONH<sub>2</sub>, CONHCH<sub>2</sub>CO<sub>2</sub>alkyl, COOalkyl, PO(OEt)<sub>2</sub> or a mono-, di- or tri-substituted phenyl group in which the substituent is COOalkyl,

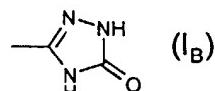
n, m and

X having the same meanings as given above in general formula I,  
 is hydrolysed in an aqueous, alcoholic or aqueous-alcoholic medium by an acid or a base.  
 (a.3) when, in formula I, W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m-$  wherein n, m and X have the same meaning as given above in general formula I, and

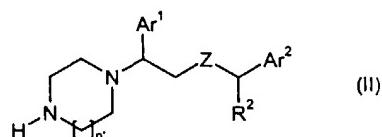
- a.3.1.  $R^1$  is CN, the corresponding compound of formula I in which  $R^1$  is  $CONH_2$  is dehydrated;
- a.3.2.  $R^1$  is  $CONH_2$ , the corresponding compound of formula I in which  $R^1$  is  $COOalkyl$  is ammonolyzed;
- a.3.3.  $R^1$  is  $COOalkyl$  or  $CONHCH_2COOalkyl$ , the corresponding compound of formula I in which  $R^1$  is  $COOH$  or  $CONHCH_2COOH$  is esterified;
- a.3.4.  $R^1$  is  $CONR^iR^{ii}$ ,  $R^i$  and  $R^{ii}$  independently representing a hydrogen atom or an alkyl group, at least one of  $R^i$  or  $R^{ii}$  being an alkyl group, the corresponding compound of formula I in which  $R^1$  is  $COOH$  or  $COOalkyl$  is aminolyzed.

These transformations may be performed under any appropriate conditions known to the person skilled in the art.

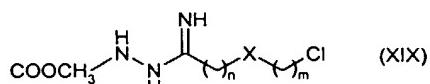
(a.4) when, in formula I, W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m-$  wherein  $R^1$  represents a triazolone of formula



and n, m and X have the same meanings as in general formula I, an  $\alpha$ -arylethylpiperazine of formula II



wherein  $Ar^1$ ,  $Ar^2$ ,  $Z$ ,  $R^2$  and  $n'$  have the same meanings as stated above is reacted under heating with a (chloromethyl)amidrazone of formula XIX



wherein n, m and X have the same meanings as stated above.

This reaction may be carried out following the method described in Ladduwahetty T. et al., J. Med. Chem. (1996), 39, 2907-2914.

(a.5) when, in formula I, W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m-$  wherein  $R^1$  is a tetrazole, n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I wherein  $R^1$  is CN is reacted with azidotrimethylsilane in the presence of dibutyltin oxide.

This transformation may be performed according to the procedure disclosed in Wittenberger S. et al., J. Org. Chem. (1993), 58, 4139-4141 or Owens A.P. et al., Bioorg. Med. Chem. Letters (1998), 8, 51-56.

(a.6) when, in formula I, W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m-$  wherein  $R^1$  represents  $CONHSO_2alkyl$ ,  $CONHSO_2phenyl$  or  $CONHSO_2tolyl$ , n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I in which  $R^1$  is  $COOH$  is reacted with a sulfonamide of formula  $R^V-SO_2-NH_2$  in which  $R^V$  represents an alkyl, phenyl or 4-methylphenyl group. This reaction may be performed under conventional peptide synthesis conditions such as, for example, those described in "Principles of Organic Synthesis" Volume 16, M. Bodansky, Springer-Verlag Berlin Heidelberg New York Tokyo 1984.

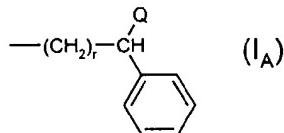
(a.7) when, in formula I, W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m$ , wherein  $R^1$  represents  $CONHSO_2alkyl$ ,

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CONHSO<sub>2</sub>phenyl or CONHSO<sub>2</sub>tolyl, n=0, X=O and m= 2, the corresponding  $\alpha$ -arylethylpiperazine of formula I wherein R<sup>1</sup> is HO-(CH<sub>2</sub>)<sub>m</sub> is reacted with the compound of formula R-SO<sub>2</sub>-N=C=O in which R represents alkyl, phenyl or 4-methylphenyl.

This reaction may, for example, be carried out under the conditions described in Friesen R.W. and Phipps L.G., Synlett (1991), 420-422.

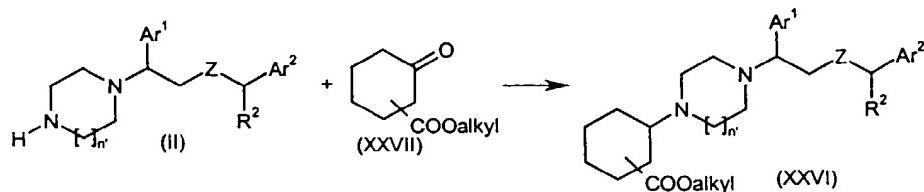
(a.8) when, in formula I, W is a group of formula



15 wherein Q=NH(CO)CH<sub>3</sub>, the corresponding compound of formula I in which Q is OH is reacted with acetonitrile in the presence of acid. The conditions used for this reaction are for example those disclosed in European Patent application 474,561 (page 37).

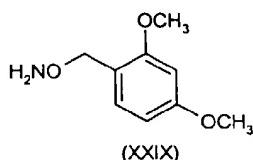
The starting compound of formula I in which Q=OH may be obtained by method a.1 described above.

20 (a.9) when, in formula I, W is a cyclohexyl group substituted by COOH, the corresponding compound of formula I in which W is a cyclohexyl group substituted by COOalkyl is hydrolysed in an aqueous, alcoholic or aqueous-alcoholic medium in presence of an acid or a base. The starting compound of formula I in which W is a cyclohexyl group substituted by COOalkyl may be obtained by reductive amination of a cyclohexanone of formula XXVII with a piperazine of formula II according to the equation



35 In these formulae, Ar<sup>1</sup>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as stated above. This reaction may for example be carried out according to the procedure disclosed in Maryanoff B.E. et al., J. Med Chem. (1981), 24 (1), 79-88.

40 (a.10) when, in formula I, W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub> wherein R<sup>1</sup> represents CONHOH, n, m and X having the same meanings as given above in general formula I, a corresponding compound of formula I wherein R<sup>1</sup> represents COOH is coupled with the compound of formula XXIX



followed by treatment with trifluoroacetic acid.

50 This reaction may be carried out according to the procedure disclosed in Barlaam B. et al., Tetrahedron Lett. (1998), 39, 7865-7868.

55 (b) when, in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOCH<sub>3</sub>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I and W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub> wherein R<sup>1</sup> represents COOalkyl, n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are bromine atoms is submitted to methoxycarbonylation by carbon monoxide treatment in the presence of palladium(II) acetate, 1,3-bis(diphenylphosphino)propane and triethylamine in meth-

anol (see Lin C.-H. et al., J. Med. Chem. (1993), 36, 2208-2218 for detailed conditions).

(c) when, in formula I, Ar<sup>1</sup> is mono-, di- or tri-substituted phenyl group in which the substituents are CN, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I and W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub> wherein R<sup>1</sup> represents COOalkyl, n, m and X having the same meanings as in general formula I, a corresponding compound of formula I Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are Bromine atoms is reacted with zinc cyanide (see Tschaen D.M. et al., J. Org. Chem. (1995), 60, 4324-4330 for detailed conditions).

(d) when in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOH or CONH<sub>2</sub>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOalkyl is hydrolysed or ammonolyzed; optionally, this transformation may take place simultaneously with hydrolysis or ammonolysis of another COOalkyl group of the compound of formula I;

(e) when in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOH, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are CN is hydrolysed; optionally, this transformation may take place simultaneously with the hydrolysis of another CN group of the compound of formula I:

(f) when in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are CN, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I and W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub> wherein R<sup>1</sup> represents COOH and n, m and X have the same meaning as stated above for general formula I, the corresponding compound of formula I in which R<sup>1</sup> is COOalkyl is hydrolysed, as described in (a2).

(g) when, in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are NH<sub>2</sub> and W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub> wherein R<sup>1</sup> represents COOH or COOalkyl, Ar<sup>2</sup>, Z, R<sup>2</sup>, n', n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are NO<sub>2</sub> is reduced. Any conditions known for the reduction of nitro groups into amino groups may be used for this transformation.

(h) when, in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are OH, W, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' having the same meaning as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are OP', wherein P' is a protecting group, is deprotected. The protecting group P' may be any suitable alcohol protecting group such as, for example, a methoxyethoxymethyl (MEM), a tetrahydropyranyl (THP), an allyl or a benzyl group. For more details concerning deprotection methods, see "Protective Groups in Organic Chemistry", J.F.W. Omie, Plenum Press, London and New York, 1973 and "Protective Groups in Organic Synthesis", Th. W. Greene, John Wiley & Sons, 1981.

(i) optionally, the α-arylethylpiperazine derivative of formula I so-obtained is converted into one of its non-toxic pharmaceutically acceptable salts. The non-toxic pharmaceutically acceptable salts can be prepared from α-arylethylpiperazine derivatives of formula I by methods which are known per se.

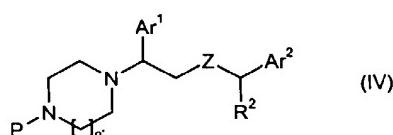
**[0022]** The compounds of formula I which are in the form of a mixture of individual optical isomers are either obtained from optically pure starting materials or by separation of a mixture of optical isomers of the compound of general formula I by conventional resolution methods, including chromatographical methods.

**[0023]** The present invention also encompasses compounds of formula II which are useful intermediates for the preparation or compounds of formula I.

**[0024]** The present invention also relates to processes for the manufacture of compounds of formula II.

**[0025]** Compounds of formula II may be prepared by one of the following processes:

(i) Compounds of formula II wherein Ar<sup>1</sup> is different from a mono-, di- or tri-sustituted phenyl group in which the substituent is NO<sub>2</sub>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' having the same meanings as in general formula II, may be obtained by classical deprotection methods of compounds of formula IV



in which P represents a protecting group, such as COOEt, tert-butoxycarbonyl or tosyl, or any other known pro-

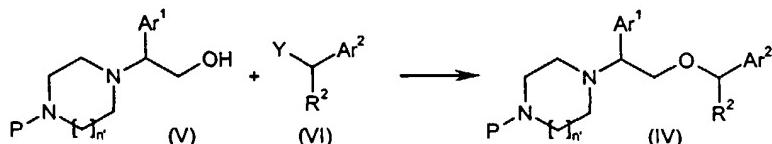
tecting group suitable for a piperazine, Ar<sup>1</sup>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' having the same meanings as in formula II. For more details concerning deprotection methods, see "Protective Groups in Organic Chemistry", J.F.W.

Omie, Plenum Press, London and New York, 1973 and "Protective Groups in Organic Synthesis, Th. W. Greene, John Wiley & Sons, 1981.

(ii) Compounds of formula II in which Ar<sub>1</sub> is a mono-, di- or tri- substituted phenyl group in which the substituent is NO<sub>2</sub>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' having the same meanings as in general formula II, may be obtained by nitration of compounds of formula II in which Ar<sub>1</sub> is a phenyl group, according to the method described in Lynch B.M., Poon L., Can. J. Chem. (1967), 45, 1431.

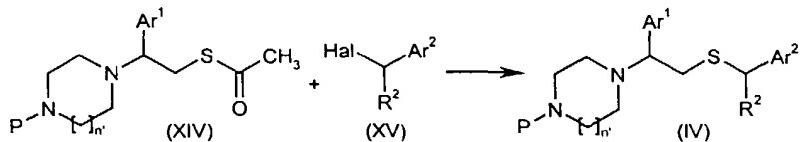
10 [0026] Compound of formula IV used for the preparation of compound of formula II may be obtained by the following methods:

- when, in formula IV, Z represents O, Ar<sup>1</sup>, Ar<sup>2</sup>, Z, n' and P having the same meanings as stated above, a compound of formula V is reacted with an alkylating agent of formula VI according to the equation



wherein Y represents a leaving group such as a halogen atom, preferably a Chlorine, a Bromine or a Iodine atom, a mesyl, a tosyl or a trichloroacetamide group, Ar<sup>1</sup>, Ar<sup>2</sup>, R<sup>2</sup>, n' and P having the same meanings as in formula IV. When Y represents a halogen atom, a mesyl or a tosyl group, this reaction is known per se and is generally carried out in an inert organic solvent, for example dimethylformamide or tetrahydrofuran, in the presence of a strong base, such as NaH and in the presence of a catalyst when Y represents a Chlorine or a Bromine atom, for example sodium iodide or potassium iodide. More exactly, the anion of compound of formula V is preformed between 0°C and room temperature; after addition of compound of formula VI, the mixture is stirred between room temperature and 50°C. When Y represents a trichloroacetamide group, the O-alkylation of compound of formula V may be carried out in the presence of a strong acid such as trifluoromethane-sulfonic acid as described in patent application WO 97/14671.

- when in formula IV Z represents S, Ar<sup>1</sup>, Ar<sup>2</sup>, Z, n' and P having the same meanings as in general formula IV, a compound of formula XIV is reacted with an alkylating agent of formula XV according to the equation



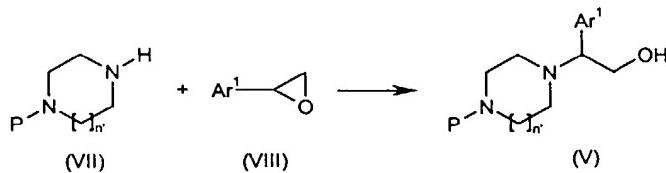
wherein Hal represents a halogen atom, preferably a Bromine atom, Ar<sup>1</sup>, Ar<sup>2</sup>, n' and P having the same meanings as stated above. This reaction is generally carried out in an inert solvent, for example toluene, dimethylformamide, an alcohol or an ether, in the presence of an organic base, for example diethylamine or pyrrolidine, or in the presence of an inorganic base, for example NaH, NaBH<sub>4</sub>, sodium hydroxide, sodium methoxide or potassium hydroxide, between -10 and 50°C.

The starting materials used for the preparation of compounds of formula IV may be prepared according to the following procedures:

- compounds of formula V may be obtained according to four different methods :

1. the reaction of a piperazine of formula VII with an epoxide derivative of formula VIII according to the equation

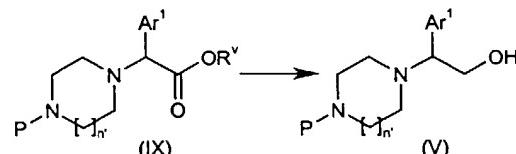
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in these formulae, Ar<sup>1</sup>, n' and P have the same meanings as stated above.

10 2. the reduction of compound of formula IX according to the equation

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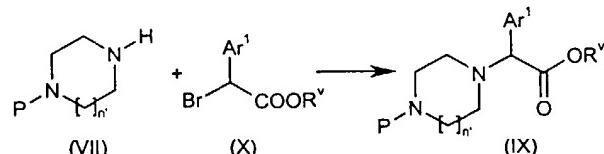


20 wherein R¹ represents a hydrogen atom or an alkyl group, Ar<sup>1</sup>, n' and P having the same meanings as stated above.

25 [0027] Compound IX may be obtained by reaction of compounds of formula VII with an α-bromo ester of formula X according to the equation

25

30



35 wherein R¹ represents a hydrogen atom or an alkyl group, Ar<sup>1</sup>, n' and P having the same meanings as stated above.

35 3. the reaction of a piperazine of formula VII with a heteroaryl boronic acid of formula XI in presence of glyoxylic acid according to the equation

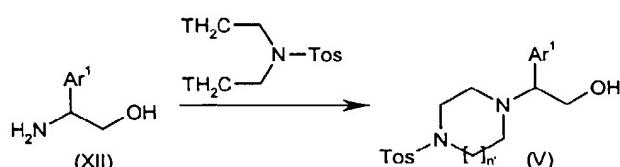
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45 wherein Ar<sup>1</sup>, n' and P have the same meanings as stated in formula V (see Petasis N.A. et al., Tetrahedron (1997), 53, 16463-16470).

4. when in formula V P is a tosyl group, Ar<sup>1</sup> and n' having the same meanings as stated above the reaction of the amine of formula XII with a disubstituted N,N-diethyl-4-methylbenzenesulfonamide according to the equation

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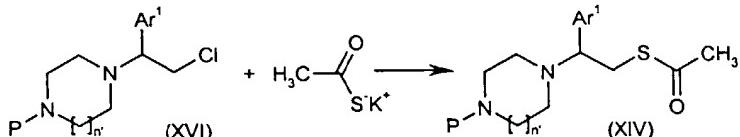
wherein Ar<sup>1</sup> and n' have the same meanings as stated above and T is a Chlorine, Bromine or Iodine atom or (4-methylphenyl)sulfonyloxy or methylsulfonyloxy group. This reaction may be carried out under the conditions disclosed in European Patent Application 617 028 A1.

5 [0028] Compounds of formula XII may be obtained by conventional reduction of the corresponding carboxylic acid.

- compounds of formula XIV may be obtained by reaction of a compound of formula XVI with a thioacetate salt, for example potassium thioacetate, according to the equation

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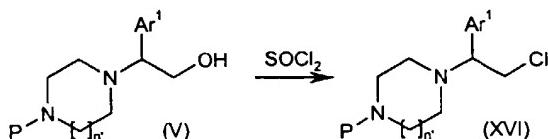
wherein Ar<sup>1</sup>, n' and P have the same meanings as stated above. This reaction is carried out in an inert solvent, for example toluene, dimethylformamide, an alcohol, ethyl acetate or dichloromethane between -10°C and 40°C.

20

[0029] Compounds of formula XVI may be obtained by halogenation of a compound of formula V in presence of thionyl chloride according to the equation

25

30



wherein Ar<sup>1</sup>, n' and P have the same meanings as stated above.

[0030] The following examples illustrate the present invention without limiting it.

[0031] Unless specified otherwise in the examples, characterization of the compounds was performed according to the following methods:

[0032] NMR spectra were recorded on a BRUKER AC 250 Fourier Transform NMR Spectrometer fitted with an Aspect 3000 computer and with a 5 mm 1H/ 13C dual probehead. The compound was studied in DMSO (or CDCl<sub>3</sub>) solution at the probe temperature of 313 K and at a concentration of 20 mg/ml. The instrument was locked on the deuterium signal of DMSO (or CDCl<sub>3</sub>). Chemical shifts are given in ppm downfield from TMS taken as internal standard.

[0033] Mass spectrometric measurements in LC/MS mode were performed as follows :

[0034] HPLC conditions

[0035] Analyses were performed using a WATERS Alliance HPLC system mounted with an INERTSIL CHROMPACK 3 ODS, DP 5 µm, 250 X 4.6 mm column.

[0036] The gradient ran from 100% solvent A (acetonitrile, water, TFA (10/90/0.1, v/v/v)) to 100% solvent B (acetonitrile, water, TFA (90/ 10/0.1, v/v/v)) in 7 min with a hold at 100% B of 4 min. The flow rate was set at 2.5 ml/min and a split of 1/10 was used just before API source. The chromatography was carried out at 30 °C.

[0037] MS conditions

[0038] Samples were dissolved in acetonitrile/water, 70/30, v/v at the concentration of about 250µgr/ml. API spectra (+ or -) were performed using a FINNIGAN (San Jose, CA, USA) LCQ ion trap mass spectrometer. APCI source operated at 450 °C and the capillary heater at 160 °C. ESI source operated at 3.5 kV and the capillary heater at 210 °C.

[0039] Mass spectrometric measurements in EI/DIP mode were performed as follows : samples were vaporized by heating the probe from 50 °C to 250 °C in 5 min. EI (Electron Impact) spectra were recorded using a FINNIGAN (San Jose, CA, USA) TSQ 700 tandem quadrupole mass spectrometer. The source temperature was set at 150 °C.

[0040] Specific rotation was recorded on a Perkin-Elmer MC241 polarimeter. The angle of rotation was recorded at 25 °C on 1% solutions in MeOH. For some molecules, the solvent was CH<sub>2</sub>C<sub>12</sub> or DMSO, due to solubility problems.

[0041] Water content is determined using a Metrohm microcoulometric Karl Fischer titrator.

[0042] Chromatographic separations are performed on silicagel 60 Merck, particle size 15-40 µm, reference 1.15111.9025.

[0043] Unless specified otherwise in the examples, the compounds are obtained as the free bases. The conversion

of these free bases into non-toxic pharmaceutically acceptable salts may proceed according to conventional methods known to those skilled in the art. The following general method are given by way of illustration.

**[0044]** For the formation of hydrochlorides or dihydrochlorides of  $\alpha$ -arylethylpiperazine derivatives of formula I, free bases were dissolved in an inert solvent, for example  $\text{CH}_2\text{Cl}_2$ , diisopropylether, and a solution of 1,2 or 3 equivalents of HCl in diethylether was added. The volatile substances were removed and the product was recrystallized, usually, from  $\text{CH}_3\text{CN}$ . The salts could also be obtained directly from acidic hydrolysis in the last step and the solid products might be obtained by lyophilisation. The exact salt composition of the product was determined by elemental analysis. The exact quantity of water was determined by Karl Fischer method.

**[0045]** For the formation of the maleates or dimaleate of  $\alpha$ -arylethylpiperazine derivatives of formula I, free bases were dissolved in 2-butanone and 1 or 2 equivalents of maleic acid were added. The solids were filtered and the products recrystallized from  $\text{CH}_3\text{CN}$ . The exact salt composition of the product was determined by elemental analysis. The exact quantity of water was determined by Karl Fischer method.

**[0046]** In the following examples,

- when the molecule contains one asymmetric center, NSA and NSB are individual optical isomers for which absolute configuration has not been determined;
- when the molecule contains two asymmetric centers, NSA and NSB refer to couple of enantiomers of which the absolute configuration has not been determined; when the absolute configuration has been determined for one or for the two asymmetric centers, the first R, S or rac. symbol refers to the absolute configuration of the Carbon atom which bears Ar<sup>1</sup>, and the second R, S or rac. symbol refers to the absolute configuration of the other asymmetric center.

Example 1. Preparation of compounds of formula I according to process (a).

#### 25 1.1. Preparation of compounds of formula V.

Method 1.

**[0047]** In a round-bottomed flask fitted with a reflux condenser and a thermometer, 15 g (125 mmoles) of (R)-phenoxyoxirane, 19.75 g (125 mmoles, 18.3 ml) of ethyl-N-piperazine carboxylate, and 80 ml of ethyl alcohol were introduced. The mixture was heated at reflux for 3 hours. Volatile substances were removed under reduced pressure and the resulting mixture was purified by chromatography on silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{aqueous ammonia } 98.5/1.5/0.5$  (v/v/V)), affording 8.8 g of (S)-4-(2-Hydroxy-1-phenyl-ethyl)-piperazine-1-carboxylic acid ethyl ester (compound 2) as a colorless oil. Yield: 25%.

**[0048]** The compounds of formula V presented in Table I were prepared according to this method.

Table I -

Compounds of formula V obtained by Method 1.				
Cpd No.	P	n'	Ar <sup>1</sup>	stereochemistry
1	COOEt	1	phenyl	racemic
3	COOEt	1	phenyl	R
4	COOEt	1	4-methylphenyl	racemic
5	COOEt	1	4-fluorophenyl	racemic
6	COOEt	1	1-naphthyl	racemic
7	COOEt	1	2-naphthyl	racemic

**[0049]** The starting oxiranes used for the preparation of compounds 4 to 7 may be obtained by the method disclosed in Bouha H. et al., Synthetic Communications (1987), 17(5), 503-513.

Method 2.

**[0050]** In a round-bottomed flask fitted with a reflux condenser and a thermometer 62.8 g (397 mmoles) of ethyl N-piperazinecarboxylate, 60.3 g (596 mmoles) of triethylamine, and 1980 ml of methyl alcohol were introduced; 109.3 g (477 mmoles) of methyl-1-bromo-1-phenylacetate were added dropwise to this mixture. The solution was heated at reflux for 24 hours. The volatile substances were removed under reduced pressure; 700 ml of methylene chloride were added to the residue; the mixture was filtered and the organic phase was washed with water and then with brine, dried

over magnesium sulfate, and concentrated under reduced pressure, affording 114 g of 4-(Methoxycarbonyl-phenyl-methyl)-piperazine-1-carboxylic acid ethyl ester as an oil. Yield: 94%.

**[0051]** In a round-bottomed flask fitted in a reflux condenser and a thermometer 57.0 g (186 mmoles) of 4-(Methoxycarbonyl-phenyl-methyl)-piperazine-1-carboxylic acid ethyl ester obtained above and 660 ml of THF were introduced under nitrogen. The solution was cooled to -20°C, and 7.0 g (185 mmoles) of lithium aluminium hydride were added portion-wise. The reaction mixture was stirred at -15°C for 45 min, cooled to -35°C; 7 ml of a 15% (w/w) solution of sodium hydroxide in water and 21 ml of water were successively added to the reaction mixture. The mixture was filtered, the precipitate was washed with THF, and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in methylene chloride (1 l) and the solution was washed with water and then brine. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure, affording 47.2 g of an oil. This oil was purified by chromatography on silica gel (eluent: methylene chloride-aqueous ammonia 98.5/1.5/0.15 (v/v)) affording 34.6 g of 4-(2-hydroxy-1-phenyl-ethyl)-piperazine-1-carboxylic acid ethyl ester (compound 1) as a yellow oil. Yield: 67%.

**[0052]** The compounds of formula V identified in Table II were prepared according to this method.

Table II -

Compounds of formula V obtained by Method 2.				
Cpd No.	P	n'	Ar <sup>1</sup>	stereo-chemistry
8	Boc	1	phenyl	racemic
9	COOEt	1	3,5-(bistrifluoromethyl)-phenyl	racemic
10	COOEt	1	4-bromophenyl	racemic
11	COOEt	1	3-chlorophenyl	racemic
12	COOEt	1	3,4-dichlorophenyl	racemic
15	COOEt	1	2,3-difluorophenyl	racemic
16	COOEt	1	3,4,5-trifluorophenyl	racemic
17	Boc	2	phenyl	racemic

**[0053]** The starting alkylating agents used for the preparation of compounds 9 to 12 and 16 may be obtained by the method described in Carini D.J. et al., J. Med. Chem. (1990), 33, 1330-1336.

**[0054]** The enantiomers of compound 12, compound 13 (NSA) and compound 14 (NSB), were obtained by resolution by chiral chromatography (Chiralcel OD, 226 nm, 23°C Eluent: iPrOH 17.5%, benzene 82.5% + DEA 0.1%), compound 13 being the compound that elutes the fastest.

### Method 3.

**[0055]** Following the procedure described in Petasis N.A. et al. in Tetrahedron (1997), 53, 16463-16470, ethyl-N-piperazine carboxylate was reacted with 3-isopropylphenyl-boron dihydioxide in the presence of glycolaldehyde to provide 4-[2-hydroxy-1-(3-isopropylphenyl)-ethyl]-piperazine-1-carboxylic acid ethyl ester (compound 18). The compounds listed in Table III were obtained by the same method.

Table III -

Compounds of formula V obtained by Method 3.				
Cpd No.	P	n'	Ar <sup>1</sup>	stereo-chemistry
19	COOEt	1	4-methoxyphenyl	racemic
20	COOEt	1	thiophen-2-yl	racemic
21	COOEt	1	thiophen-3-yl	racemic
22	COOEt	1	furan-2-yl	racemic
23	COOEt	1	benzo[c]thiophen-1-yl	racemic
24	COOEt	1	isobenzofuran-1-yl	racemic

### Method 4.

**[0056]** 2-Phenyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethanol (compound 25) was obtained from 2-phenylethan-1-olamine and N,N-bis(chloroethyl)-4-methylbenzenesulfonamide following the method described in European Patent

Application 617 028 A1. When starting from (S) or (R) 2-phenylethan-1-olamine, the corresponding (S) or (R) 2-Phenyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethanol (compounds 26 and 27, respectively) were obtained.

1.2. Preparation of compounds of formula IV.

5      1.2.1. Preparation of compounds of formula IV wherein Z is O.

[0057] In a round-bottomed flask fitted with a reflux condenser and a thermometer 8.8 g (32 mmoles) of (S)-4-(2-Hydroxy-1-phenyl-ethyl)-piperazine-1-carboxylic acid ethyl ester (compound 2 prepared at example 1.1) and 50 ml of THF were introduced. The solution was cooled to 0°C and 1.5 g of sodium hydride (47 mmoles, 78% in parafin) were added portionwise. The solution was allowed to reach room temperature and was stirred for 30 minutes. The solution was cooled again to 0°C, and a solution of 8.5 g (32 mmoles) of 3,5-bis-(trifluoromethyl)-benzyl chloride in 20 ml of THF was added dropwise. Sodium iodide (4.7 g, 32 mmoles) was added to the mixture, which was then stirred at room temperature for 24 hours. The mixture was then cooled to 0°C and the reaction was quenched with 20 ml of aqueous ammonium chloride. The volatile substances were removed under reduced pressure, 100 ml of water were added, and the pH was adjusted to 11 by addition of aqueous sodium hydroxide. The mixture was extracted with diethyl ether, the organic phase was dried over magnesium sulfate, and concentrated under reduced pressure, affording 15.4 g of an oil. This oil was purified by chromatography on silica gel (eluent: methylene chloride-methanol-aqueous ammonia 99/1/0.5 (v/v/v)), affording 9.5 g of (S)-4-[2-(3,5-bis-[trifluoromethyl]-benzyloxy)-1-phenyl-ethyl]-piperazine-1-carboxylic acid ethyl ester (compound 30) as a yellow oil. Yield: 60%.

10      [0058] The compounds listed in Table IV were obtained by the same method. When R<sup>3</sup> represents CH<sub>3</sub>, the starting alkylating agents used according to this method may be obtained by the method disclosed in Owens A.P. et al., Bio. Med. Chem. Lett. (1995), 5, 2761-2766.

15      25

20      30

25      35

30      40

35      45

40      50

45      55

Table IV – Preparation of compounds of formula IV wherein Z is O

Cpd No.	P	n	R <sup>2</sup>	Ar <sup>1</sup>	Ar <sup>2</sup>	stereochemistry	starting cpd No.
28	Boc	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	racemic	8
29	COOEt	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	racemic	1
30	COOEt	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	R	3
31	Tos	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	racemic	25
32	Tos	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	S	26
33	Tos	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	R	27
34	COOEt	1	H	4-methylphenyl	3,5-bis(trifluoromethyl)phenyl	racemic	4
35	COOEt	1	H	3-isopropylphenyl	3,5-bis(trifluoromethyl)phenyl	racemic	18
36	COOEt	1	H	4-methoxyphenyl	3,5-bis(trifluoromethyl)phenyl	racemic	19
37	COOEt	1	H	3-chlorophenyl	3,5-bis(trifluoromethyl)phenyl	racemic	11
38	COOEt	1	H	4-bromophenyl	3,5-bis(trifluoromethyl)phenyl	racemic	10
39	COOEt	1	H	4-fluorophenyl	3,5-bis(trifluoromethyl)phenyl	racemic	5
40	COOEt	1	H	3,4-dichlorophenyl	3,5-bis(trifluoromethyl)phenyl	racemic	12
41	COOEt	1	H	3,4,5-trifluorophenyl	NSA	13	
42	COOEt	1	H	3,4-dichlorophenyl	NSB	14	
43	COOEt	1	H	2,3-difluorophenyl	3,5-bis(trifluoromethyl)phenyl	racemic	15
44	COOEt	1	H	3,4,5-trifluorophenyl	racemic	16	
45	COOEt	1	H	1-naphthyl	3,5-bis(trifluoromethyl)phenyl	racemic	6
46	COOEt	1	H	2-naphthyl	3,5-bis(trifluoromethyl)phenyl	racemic	7
47	COOEt	1	H	thiophen-2-yl	3,5-bis(trifluoromethyl)phenyl	racemic	20
48	COOEt	1	H	thiophen-3-yl	3,5-bis(trifluoromethyl)phenyl	racemic	21
49	COOEt	1	H	furan-2-yl	3,5-bis(trifluoromethyl)phenyl	racemic	22
50	COOEt	1	H	benzol[c]thiophen-1-yl	3,5-bis(trifluoromethyl)phenyl	racemic	23
51	COOEt	1	H	isobenzofuran-1-yl	3,5-bis(trifluoromethyl)phenyl	racemic	24
52	COOEt	1	H	phenyl	2,4-bis(trifluoromethyl)phenyl	racemic	1
53	COOEt	1	H				

Table IV (continued) – Preparation of compounds of formula IV wherein Z is O

Cpd No.	P	n'	R2	Ar1	Ar2	stereochemistry	starting cpd No.
54	COOEt	1	H	phenyl	3,5-dimethylphenyl	racemic	1
55	COOEt	1	H	phenyl	3,5-bis(tert-butyl)phenyl	racemic	1
56	COOEt	1	H	phenyl	2-methoxyphenyl	racemic	1
57	COOEt	1	H	phenyl	3-isopropoxyphenyl	racemic	1
58	COOEt	1	H	phenyl	2-trifluoromethoxyphenyl	racemic	1
59	COOEt	1	H	phenyl	3,4,5-trimethoxyphenyl	racemic	1
60	Tos	1	H	phenyl	3-chlorophenyl	racemic	25
61	COOEt	1	H	phenyl	3,5-dichlorophenyl	racemic	1
62	Tos	1	H	phenyl	3,5-dichlorophenyl	S	26
63	Tos	1	H	phenyl	3,5-dichlorophenyl	R	27
64	COOEt	1	H	phenyl	3,4-dichlorophenyl	racemic	1
65	Tos	1	H	phenyl	3,5-dibromophenyl	racemic	25
66	Tos	1	H	phenyl	3,5-difluorophenyl	racemic	25
67	Boc	1	H	phenyl	3-bromo-5-iodophenyl	racemic	8
68	Boc	1	H	phenyl	3,5-dichloro-4-methoxyphenyl	racemic	8
69	COOEt	1	H	3,5-bis(trifluoromethyl)phenyl	phenyl	racemic	9
70	COOEt	1	CH3	3,5-bis(trifluoromethyl)phenyl	phenyl	racemic	1
73	Tos	1	CH3	3,5-bis(trifluoromethyl)phenyl	phenyl	racemic	25
76	Tos	1	CH3	3,5-bis(trifluoromethyl)phenyl	phenyl	S, rac.	26
79	Tos	1	CH3	3,5-bis(trifluoromethyl)phenyl	phenyl	R, rac.	27
82	Boc	2	H	3,5-bis(trifluoromethyl)phenyl	phenyl	racemic	17

[0059] The following racemic mixtures were resolved into their isomers by chromatographic separation on silica gel 60 or on chiral stationary phases:

- compound 70: stationary phase: silica gel 60; eluent:  $\text{CH}_2\text{Cl}_2$ ; the individual enantiomers so-obtained will be referred to as compounds 71 (NSA) and 72 (NSB), 71 being the compound that elutes the fastest under the given conditions;
- compound 73: stationary phase: silica gel 60; eluent: benzine 40%,  $\text{CH}_2\text{Cl}_2$  60%; the individual isomers so-obtained will be referred to as compounds 74 (NSA) and 75 (NSB), 74 being the compound that elutes the fastest.
- compound 76: stationary phase: CHIRALPAK AD, detection at 226 nm; temperature 20°C; eluent: ethanol 5%, benzine 95%, diethylamine 0.1%; the individual diastereoisomers so-obtained will be referred to as compounds 77 (S,R) and 78 (S,S), 77 being the compound that elutes the fastest.
- compound 79: stationary phase: silica gel 60; eluent: benzine 40%,  $\text{CH}_2\text{Cl}_2$  60%; the individual diastereoisomers so-obtained will be referred to as compounds 80 (R,R) and 81 (R,S), 80 being the compound that elutes the slowest.

15 1.2.2. Preparation of compounds of formula IV wherein Z is S.

**[0060]**

a. In a round-bottomed flask fitted with a reflux condenser and a thermometer 6.3 g (17.5 mmoles) of 2-phenyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethanol (compound 25 prepared at example 1.1) and 20 ml of methanol are introduced. An excess of 3 N methanolic HCl is added dropwise, the volatile substances are removed under reduced pressure, affording the dihydrochloride salt of 2-phenyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethanol. To the salt are added 250 ml of  $\text{CHCl}_3$ , the mixture is cooled to 0°C, and 4.7 g (39.5 mmoles) of  $\text{SOCl}_2$  are added dropwise. After completion of the addition, the mixture is heated at reflux for 3 hours. The volatile substances are removed under reduced pressure, affording crude 1-(2-chloro-1-phenyl-ethyl)-4-(toluene-4-sulfonyl)-piperazine as an oil. Ethyl alcohol (300 ml), 2.5 g (22.2 mmoles) of potassium thioacetate, and 3.07 g (22.2 mmoles) of potassium carbonate are then added to this crude product. The mixture is stirred for 16 hours, and the volatile substances are removed under reduced pressure. 150 ml of ether and 150 ml of water are added to the residue, and the mixture is filtered, affording the crude thioacetic acid S-[2-phenyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethyl] ester (compound 83) as a white solid. The aqueous phase is extracted three times with methylene chloride. The solid is dissolved in methylene chloride, the methylene chloride solutions are combined and washed with brine, dried over magnesium sulfate and concentrated under reduced pressure, affording 4.32 gr of compound 83 as a white solid. Yield: 59%.

b. In a round-bottomed flask fitted with a reflux condenser and a thermometer 2.76 g (6.6 mmoles) of thioacetate 83 and 250 ml of degassed methyl alcohol are introduced. The mixture is cooled to 0°C and 356 mg (6.6 mmoles) of sodium methylate are added. The mixture is stirred under argon for one hour at 0°C, and 1.9 g (7.26 mmoles) of 3,5-bis-trifluoromethyl-benzyl bromide are added. The mixture is stirred for 48 hours, volatile substances are removed under reduced pressure, and 100 ml of water are added. The aqueous phase is extracted three times with methylene chloride, the combined organic phases are washed with brine and dried over magnesium sulfate. Volatile substances are removed under reduced pressure, affording 4.54 g of crude 1-[2-(3,5-bis-trifluoromethyl-benzylsulfanyl)-1-phenyl-ethyl]-4-(toluene-4-sulfonyl)-piperazine (compound 84) as a colorless oil. This oil was purified by chromatography on silica gel (eluent : methylene chloride-hexane 65/35 (v/v)), affording 3.26 g of compound 84 as a colorless oil. Yield: 82%.

45 [0061] 1-[2-(3,5-Dimethyl-benzylsulfanyl)-1-phenyl-ethyl]-4-(toluene-4-sulfonyl)-piperazine (compound 85) was obtained by the same method.

1.3. Preparation of compounds of formula II.

50 [0062] 1.3.1. Preparation of compounds of formula II wherein Ar1 is not a mono-, di- or tri-substituted phenyl group in which the substituent is  $\text{NO}_2$ .

[0063] The compounds of formula II summarized in Table V are obtained by classical deprotection methods of corresponding compounds of formula IV. For more details concerning deprotection methods, see "Protective Groups in Organic Chemistry", J.F.W. Omie, Plenum Press, London and New York, 1973 and "Protective Groups in Organic Synthesis", Th. W. Greene, John Wiley & Sons, 1981.

[0064] Physico-chemical properties of the compounds of formula II prepared according to this method are given in Table Va below. When the compounds of formula II are in the form of non toxic pharmaceutically acceptable salts, they are obtained by the general method stated above.

Table V - Preparation of compounds of formula II by deprotection of compounds of formula IV

Cpd No.	n'	R2	Ar1	Ar2	Z	Stereochemistry	Starting cpd No.
86	1	H	phenyl phenyl phenyl 4-methylphenyl	3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl	O	racemic	28, 29 or 32
87	1	H			O	S	30 or 33
88	1	H			O	R	31 or 34
89	1	H			O	racemic	35
90	1	H			O	racemic	36
91	1	H			O	racemic	37
92	1	H			O	racemic	38
93	1	H			O	racemic	39
94	1	H			O	racemic	40
95	1	H			O	racemic	41
96	1	H			NSA		42
97	1	H			NSB		43
98	1	H			O	racemic	44
99	1	H			O	racemic	45
100	1	H			O	racemic	46
101	1	H			O	racemic	47
102	1	H	3,4,5-trifluorophenyl 1-naphthyl 2-naphthyl thiophen-2-yl thiophen-3-yl furan-2-yl	3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl 3,5-bis(trifluoromethyl)phenyl	O	racemic	48
103	1	H			O	racemic	49
104	1	H			O	racemic	50
105	1	H			O	racemic	51
106	1	H			O	racemic	52
107	1	H			O	racemic	53
108	1	H			O	racemic	54
109	1	H			O	racemic	55
110	1	H			O	racemic	56
111	1	H			O	racemic	57

Table V (continued)– Preparation of compounds of formula II by deprotection of compounds of formula IV

Cpd No.	n'	R2	Ar1	Ar2	Z	Stereochemistry	Starting cpd No.
112	1	H	phenyl	2-trifluoromethoxyphenyl	O	racemic	58
113	1	H	phenyl	3,4,5-trimethoxyphenyl	O	racemic	59
114	1	H	phenyl	3-chlorophenyl	O	racemic	60
115	1	H	phenyl	3,5-dichlorophenyl	O	racemic	61
116	1	H	phenyl	3,5-dichlorophenyl	O	S	62
117	1	H	phenyl	3,5-dichlorophenyl	O	R	63
118	1	H	phenyl	3,4-dichlorophenyl	O	racemic	64
119	1	H	phenyl	3,5-dibromophenyl	O	racemic	65
120	1	H	phenyl	3,5-difluorophenyl	O	racemic	66
121	1	H	phenyl	3-bromo-5-iodophenyl	O	racemic	67
122	1	H	3,5-bis(trifluoromethyl)phenyl	3,5-dichloro-4-methoxyphenyl	O	racemic	68
123	1	H	3,5-bis(trifluoromethyl)phenyl	phenyl	O	racemic	69
124	1	CH3	phenyl	3,5-bis(trifluoromethyl)phenyl	O	NSA	71
125	1	CH3	phenyl	3,5-bis(trifluoromethyl)phenyl	O	NSB	72 or 75
126	1	CH3	phenyl	3,5-bis(trifluoromethyl)phenyl	O	S, R	77
127	1	CH3	phenyl	3,5-bis(trifluoromethyl)phenyl	O	S, S	78
128	1	CH3	phenyl	3,5-bis(trifluoromethyl)phenyl	O	R, R	80
129	1	CH3	phenyl	3,5-bis(trifluoromethyl)phenyl	O	R, S	81
130	2	H	phenyl	3,5-bis(trifluoromethyl)phenyl	O	racemic	82
131	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	S	racemic	84
132	1	H	phenyl	3,5-dimethylphenyl	S	racemic	85

Table Va -

<u>Physico-chemical properties of compounds of formula II.</u>			
	Cpd No.	Free base/salt	Physico-chemical properties
5	86		- <sup>1</sup> H-NMR (DMSO): 7.94 (s, 1H), 7.85 (s, 2H), 7.4-7.2 (m, 5H), 4.65 (s, 2H), 3.92 (dd, 1H), 3.78 (dd, 1H), 3.59 (t, 1H), 2.75-2.55 (m, 4H), 2.45-2.2 (m, 4H). - Mass: (LC/MS APCI+): 433 (MH+).
10	90	2 HCl . 3/4 H <sub>2</sub> O	- <sup>1</sup> H-NMR (DMSO): 8.02 (s, 1H), 7.94 (s, 2H), 7.37 (s, 1H), 7.34 (m, 2H), 7.31 (t, 1H), 4.74 (s, 2H), 4.59 (m, 1H), 4.32 (m, 1H), 4.05 (m, 1H), 3.41 (m, 8H), 2.89 (m, 1H), 1.21 (d, 6H). - Mass: (LC/MS APCI+): 475 (MH+).
15	91	2 HCl . 1 H <sub>2</sub> O	- <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.84 (s, 2H), 7.4 (d, 2H), 6.95 (d, 2H), 4.7 (dd, 2H), 4.47 (t, 1H), 4.1-3.9 (m, 2H), 3.73 (s, 3H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : (LC/MS APCI+): 463 (MH+).
20	92	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.9 (s, 1H), 7.75 (s, 2H), 7.35-7.2 (m, 4H), 6.18(s, 4H), 4.6 (s, 2H), 4.0-3.65 (m, 3H), 3.0 (m, 4H), 2.6 (m, 4H). - Mass : (LC/MS APCI+): 467/469 (MH+).
25	94	2 HCl . 2/3 H <sub>2</sub> O	- <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.81 (s, 2H), 7.52 (dd, 2H), 7.2 (d+d, 2H), 4.75 (s, 2H), 4.44 (t, 1H), 4.1-3.95 (m, 2H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : (LC/MS APCI+): 451 (MH+).
30	95	2 HCl	- <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.76 (s, 2H), 7.64 (d, 1H), 7.58 (d, 1H), 7.38 (dd, 1H), 4.65 (s, 2H), 4.08 (t, 1H), 3.91 (d, 2H), 3.25-3.15 (m, 4H), 3.0-2.7 (m, 4H). - Mass : (LC/MS APCI+): 501/503/505 (MH+).
35	98	1 maleate	- <sup>1</sup> H-NMR (DMSO): 8.2 (s, 2H), 8.0 (s, 1H), 7.8 (s, 2H), 7.3 (m, 1H), 7.2 (m, 2H), 6.0 (s, 2H), 4.7 (m, 2H), 4.2 (m, 1H), 4.0 (m, 1H), 3.9 (m, 1H), 2.0-2.5 (m, 8H). - Mass : (LC/MS APCI+): 469 (MH+).
40	100	2 HCl	- <sup>1</sup> H-NMR (DMSO): 8.21 (d, 1H), 7.92 (d, 2H), 7.83 (s, 1H), 7.7 (d+s, 3H), 7.6-7.4 (m, 3H), 5.05 (t, 1H), 4.64 (s, 2H), 4.15-3.95 (m, 2H), 3.85-3.65 (m, 6H), 3.15-2.95 (m, 2H). - Mass : (EI/DIP): 482 (M+).
45	101		- <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 7.82 (dd, 3H), 7.74 (s, 2H), 7.65 (s, 2H), 7.45 (dd, 3H), 4.57 (s, 2H), 3.95 (dd, 1H), 3.85 (dd, 1H), 3.72 (t, 1H), 2.95 (m, 4H), 2.6-2.4 (m, 4H). - Mass : (LC/MS APCI+): 483 (MH+).
50	107		- <sup>1</sup> H-NMR (DMSO): 7.97 (d, 1H), 7.92 (s, 1H), 7.75 (d, 1H),
55			

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Table Va - (continued)

<u>Physico-chemical properties of compounds of formula II.</u>		
Cpd No.	Free base/salt	Physico-chemical properties
5		7.35-7.15 (m, 5H), 4.7 (s, 2H), 3.92 (dd, 1H), 3.78 (dd, 1H), 3.57 (t, 1H), 2.75-2.55 (m, 4H), 2.45-2.2 (m, 4H). - Mass : (LC/MS APCI+): 433 (MH+).
10	108	- <sup>1</sup> H-NMR (DMSO): 7.35-7.15 (m, 5H), 6.87 (s, 1H), 6.79 (s, 2H), 4.43 (s, 2H), 3.78 (dd, 1H), 3.66 (dd, 1H), 3.53 (t, 1H), 2.75-2.55 (m, 4H), 2.45-2.2 (m, 4H), 2.22 (s, 6H). - Mass : (LC/MS APCI+): 325 (MH+).
15	109	2 maleate - <sup>1</sup> H-NMR (DMSO): 7.29 (m, 5H), 7.24 (s, 1H), 6.99 (s, 2H), 6.17 (s, 2H), 4.40 (m, 1H), 3.95-3.6 (m, 4H), 3.04 (m, 4H), 2.65-2.5 (m, 4H), 1.19 (s, 9H). - Mass : (LC/MS APCI+): 409 (MH+).
20	110	- <sup>1</sup> H-NMR (DMSO): 7.35-7.15 (m, 7H), 6.95 (d, 1H), 6.88 (t, 1H), 4.44 (s, 2H), 3.9-3.6 (m, 2H), 3.75 (s, 1H), 3.55 (t, 1H), 3.41 (s, 3H), 2.75-2.55 (m, 4H), 2.45-2.2 (m, 4H). - Mass : (LC/MS APCI+): 327 (MH+).
25	112	 - <sup>1</sup> H-NMR (DMSO): 7.45-7.15 (m, 9H), 4.55 (s, 2H), 3.85 (dd, 1H), 3.75 (dd, 1H), 3.55 (t, 1H), 2.75-2.55 (m, 4H), 2.45-2.2 (m, 4H). - Mass : (LC/MS APCI+): 381 (MH+).
30	113	 - <sup>1</sup> H-NMR (DMSO): 7.35-7.2 (m, 5H), 6.51 (d, 2H), 4.36 (d, 2H), 3.9-3.5 (m, 3H), 3.71 (s, 6H), 3.64 (s, 3H), 3.0-2.4 (m, 8H). - Mass : (LC/MS APCI+): 387 (MH+).
35	114	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.4-7.25 (m, 9H), 4.45 (s, 2H), 3.85 (m, 1H), 3.8-3.55 (m, 2H), 3.7-3.1 (m, 8H). - Mass: (LC/MS APCI): 331/333 (MH+).
40	115	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.55-7.4 (m, 5H), 7.4 (s, 1H), 7.25 (s, 2H), 4.53 (dd, 2H), 4.45 (t, 1H), 4.1-3.8 (m, 2H), 3.4-3.2 (m, 6H), 3.2-3.0 (m, 2H). - Mass : (LC/MS APCI+): 365/367/369 (MH+).
45	118	 - <sup>1</sup> H-NMR (DMSO): 7.55 (d, 1H), 7.4 (d, 1H), 7.4-7.15 (m, 6H), 4.45 (s, 2H), 3.85 (dd, 1H), 3.73 (dd, 1H), 3.55 (t, 1H), 2.75-2.55 (m, 4H), 2.45-2.2 (m, 4H). - Mass : (LC/MS APCI+): 365/367/369 (MH+).
50	119	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.65 (s, 1H), 7.4 (m, 6H), 4.52 (s, 2H), 4.41 (t, 1H), 4.1-3.9 (m, 2H), 3.5-3.2 (m, 6H), 3.2-3.0 (m, 2H). - Mass : (LC/MS APCI): 453/455/457 (MH+).
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Table Va - (continued)

Physico-chemical properties of compounds of formula II.		
Cpd No.	Free base/salt	Physico-chemical properties
5	120	- <sup>1</sup> H-NMR (DMSO): 7.65 (m, 1H), 7.45 (m, 2H), 7.2-7.0 (m, 5H), 4.7-4.5 (m, 1H), 4.6 (s, 2H), 4.3 (m, 1H), 4.0 (m, 1H), 3.6-3.1 (m, 8H). - Mass : (LC/MS APCI): 333 (MH+)
10	121	- <sup>1</sup> H-NMR (DMSO): 7.8 (s, 1H), 7.6 (s, 1H), 7.4 (s, 1H), 7.3 (m, 5H), 6.1 (s, 2H), 4.5 (s, 2H), 3.8 (m, 3H), 2.6-3.0 (m, 8H). - Mass : (LC/MS APCI): 501/503 (MH+).
15	122	- <sup>1</sup> H-NMR (DMSO): 7.5-7.4 (m, 5H), 7.3 (s, 2H), 4.47 (s, 2H), 4.4 (t, 1H), 4.1-3.85 (m, 2H), 3.75 (s, 3H), 3.35-3.2 (m, 6H), 3.1 (m, 2H). - Mass : (LC/MS APCI+): 395/397/399 (MH+).
20	130	- <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 7.78 (s, 1H), 7.68 (s, 2H), 7.29 (m, 5H), 4.60 (s, 2H), 4.1-3.9 (m, 2H), 3.85 (m, 1H), 3.30 (m, 2H), 3.12 (m, 2H), 3.03 (m, 2H), 2.87 (m, 4H), 2.05 (m, 2H). - Mass : (LC/MS APCI+): 447 (MH+).
25	131	- <sup>1</sup> H-NMR (DMSO): 7.75 (s, 1H), 7.65 (s, 2H), 7.2-7.1 (m, 5H), 4.2 (t, 1H), 4.1-3.8 (dd, 2H), 3.3 (m, 2H), 3.2 (m, 4H), 3.1 (m, 4H). - Mass : (LC/MS ESI +): 449 (MH+).
30	132	- <sup>1</sup> H-NMR (DMSO): 7.35 (m, 5H), 6.82 (s, 1H), 6.74 (s, 2H), 4.15 (t, 1H), 3.54 (s, 2H), 3.45-3.0 (m, 10H), 2.16 (s, 6H). - Mass : (LC/MS ESI +): 341 (MH+).
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1.3.2. Preparation of compounds of formula II wherein Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituent is NO<sub>2</sub>.

[0065] 1-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(2-nitro-phenyl)-ethyl]-piperazine (compound 133) was obtained by nitration of 1-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazine (compound 86 prepared at example 1.3.1 above) according to the method described in Lynch B.M., Poon L., Can. J. Chem. (1967), 45, 1431.

#### 1.4. Preparation of compounds of formula I.

##### 1.4.1. Preparation of compounds of formula I according to process (a.1).

[0066] In a round-bottomed flask fitted with a reflux condenser and a thermometer 7.5 g (17 mmoles) of 1-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazine (compound 86 prepared at example 1.3.1 above), 60 ml of DMF and 7.2 g (52 mmoles) of potassium carbonate were introduced. The resulting mixture was cooled to 5°C, and a solution of 5 g (31 mmoles) of 5-bromo-valeronitrile in 10 ml of DMF was added dropwise. The reaction mixture was stirred at 5°C for 5 hours, and volatile substances were removed under reduced pressure. Methylene chloride (50 ml) was added, the organic phase was washed twice with water, dried over magnesium sulfate, and concentrated under reduced pressure, affording 11.3 g of an oil. This oil was purified by chromatography on silica gel (eluent : methylene chloride-methanol-aqueous ammonia 98.5/1.5/0.15 (v/v)), affording 7.2 g of {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 134) as an oil. Yield: 80%.

[0067] The compounds listed in Table VI were obtained by this method.

[0068] Physico-chemical properties of the compounds of formula I prepared according to this method are given in Table VIa below. When the compounds of formula I are in the form of non toxic pharmaceutically acceptable salts, they are obtained by the general methods given above.

[0069] The following racemic mixtures were resolved into their individual enantiomers by chromatography using a chiral stationary phase:

- compound 175: stationary phase: CHIRALPAK AD, detection at 226 nm; temperature 30°C; eluent: ethanol 10%, benzine 90%, diethylamine 0.1%; the individual isomers so-obtained will be referred to as compounds 176 (NSA) and 177 (NSB), 176 being the compound that elutes the fastest;
- compound 181: stationary phase: CHIRALCEL OJ, detection at 226 nm; temperature 30°C; eluent: isopropanol 5%, benzine 95%, diethylamine 0.1%; the individual isomers so-obtained will be referred to as compounds 182 (NSA) and 183 (NSB), 182 being the compound that elutes the fastest;
- compound 214: stationary phase: CHIRALPAK AS, detection at 226 nm; temperature 30°C; eluent: ethanol 10%, benzine 90%, diethylamine 0.1%; the individual isomers so-obtained will be referred to as compounds 215 (S,R) and 218 (R,S), 215 being the compound that elutes the slowest;
- compound 224: stationary phase: CHIRALCEL OJ, detection at 226 nm; temperature: room temperature; eluent: ethanol 5%, benzine 95%, diethylamine 0.1%; the individual isomers so-obtained will be referred to as compounds 225 (NSA) and 226 (NSB), 225 being the compound that elutes the fastest.

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Table VI- Compound of formula I by process (a.1)

Cpd No.	Stereo-chemistry	n'	R2	Ar1	Ar2	Z	W	Starting cpd No.
134	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	86
135	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	86
136	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	iPrO(CO)CH <sub>2</sub> -	87
137	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	tBuO(CO)CH <sub>2</sub> -	87
138	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	EtO(CO)(CH <sub>2</sub> ) <sub>3</sub> -	86
139	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)(CH <sub>2</sub> ) <sub>4</sub> -	86
140	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)(CH <sub>2</sub> ) <sub>4</sub> -	86
141	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	EtO(CO)(CH <sub>2</sub> ) <sub>5</sub> -	86
142	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	iPrO(CO)(CH <sub>2</sub> ) <sub>5</sub> -	86
143	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> -	86
144	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> -	87
145	R	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> -	88
146	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)(CH <sub>2</sub> ) <sub>2</sub> -	87
147	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	86
148	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	87
149	R	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	88
150	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)(CH <sub>2</sub> ) <sub>2</sub> -	86
151	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	NC(CH <sub>2</sub> ) <sub>3</sub> -	86
152	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	NC(CH <sub>2</sub> ) <sub>4</sub> -	86
153	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	NC(CH <sub>2</sub> ) <sub>4</sub> -	87
154	R	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	NC(CH <sub>2</sub> ) <sub>4</sub> -	88
155	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	NC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	86
156	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	NC(CH <sub>2</sub> ) <sub>5</sub> -	86
157	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	HO(CH <sub>2</sub> ) <sub>2</sub> -	86
158	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	HO(CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	87
159	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	HO <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub> -	86
160	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	HO <sub>3</sub> S(CH <sub>2</sub> ) <sub>3</sub> -	86
161	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	2-(4-thiomorpholino 1,1-dioxide)ethyl	86

Table VI- Compound of formula I by process (a.1)

Cpd No.	Stereochemistry	n'	R2	Ar1	Ar2	Z	W	Starting cpd No.
162	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	2-(N-morpholino)ethyl	86
163	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	(EtO <sub>2</sub> PO)(CH <sub>2</sub> ) <sub>2</sub> -	86
164	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	(EtO <sub>2</sub> PO)(CH <sub>2</sub> ) <sub>2</sub> -	87
165	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	2-(EtO(CO))-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	86
166	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	3-(MeOCO))-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	86
167	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	4-(MeOCO))-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	87
168	S,NS	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	C <sub>6</sub> H <sub>5</sub> CH(COO <i>Me</i> )-	87
169	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	C <sub>6</sub> H <sub>5</sub> CH(OH)(CH <sub>2</sub> ) <sub>2</sub> -	86
170	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	2-pyridinyl-CH <sub>2</sub> -	86
171	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	N-phthalimidyl-[CH <sub>2</sub> ] <sub>2</sub> -	86
172	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	3,4,5-trimethoxyphenyl-methyl	86
173	S	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	3,4,5-trimethoxyphenyl-methyl	87
174	R	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	3,4,5-trimethoxyphenyl-methyl	88
175	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	0	3,4,5-trimethoxyphenyl-methoxy-2-ethyl-	86
178	racemic	1	H	4-methylphenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	89
179	racemic	1	H	3-isopropylphenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	90
180	racemic	1	H	4-methoxyphenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	91
181	racemic	1	H	3-chlorophenyl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	92
184	racemic	1	H	4-bromophenyl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	93
185	racemic	1	H	4-fluorophenyl	3,5-bis(trifluoromethyl)phenyl	0	NC(CH <sub>2</sub> ) <sub>4</sub> -	94
186	NSA	1	H	3,4-dichlorophenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	96
187	NSB	1	H	3,4-dichlorophenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	97
188	racemic	1	H	2,3-difluorophenyl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	98
189	racemic	1	H	3,4,5-trifluorophenyl	3,5-bis(trifluoromethyl)phenyl	0	Eto(CO)CH <sub>2</sub> -	99
190	racemic	1	H	2-nitrophenyl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	134
191	racemic	1	H	1-naphthyl	3,5-bis(trifluoromethyl)phenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> -	100
192	racemic	1	H	thiophen-2-yl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	102
193	racemic	1	H	thiophen-3-yl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	103

Table VI- Compound of formula I by process (a.1)

Cpd No.	Stereocchemistry	n	R2	Ar1	Ar2	Z	W	Starting cpd No.
194	racemic	1	H	furan-2-yl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	104
195	racemic	1	H	benzo[c]thiophen-1-yl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	105
196	racemic	1	H	isobenzofuran-1-yl	3,5-bis(trifluoromethyl)phenyl	0	MeO(CO)CH <sub>2</sub> -	106
197	racemic	1	H	phenyl	3,5-dimethylphenyl	0	MeO(CO)CH <sub>2</sub> -	108
198	racemic	1	H	phenyl	2-methoxyphenyl	0	MeO(CO)CH <sub>2</sub> -	110
199	racemic	1	H	phenyl	3-isopropoxyphenyl	0	MeO(CO)CH <sub>2</sub> -	111
200	racemic	1	H	phenyl	3,4,5-trimethoxyphenyl	0	H <sub>2</sub> N(CO)CH <sub>2</sub> -	113
201	racemic	1	H	phenyl	3-chlorophenyl	0	Eto(CO)CH <sub>2</sub> -	114
202	racemic	1	H	phenyl	3,5-dichlorophenyl	0	MeO(CO)CH <sub>2</sub> -	115
203	S	1	H	phenyl	3,5-dichlorophenyl	0	Eto(CO)CH <sub>2</sub> -	116
204	R	1	H	phenyl	3,5-dichlorophenyl	0	Eto(CO)CH <sub>2</sub> -	117
205	racemic	1	H	phenyl	3,4-dichlorophenyl	0	MeO(CO)CH <sub>2</sub> -	118
206	racemic	1	H	phenyl	3,5-dibromophenyl	0	Eto(CO)CH <sub>2</sub> -	119
207	racemic	1	H	phenyl	3,5-difluorophenyl	0	Eto(CO)CH <sub>2</sub> -	120
208	racemic	1	H	phenyl	3-bromo-5-iodophenyl	0	MeO(CO)CH <sub>2</sub> -	121
209	racemic	1	H	3,5-bis(trifluoromethyl)-phenyl	phenyl	0	Eto(CO)CH <sub>2</sub> -	123
210	NSA	1	CH <sub>3</sub>				MeO(CO)CH <sub>2</sub> -	124
211	NSB	1	CH <sub>3</sub>				MeO(CO)CH <sub>2</sub> -	125
212	NSA	1	CH <sub>3</sub>				NC(CH <sub>2</sub> ) <sub>4</sub> -	124
213	NSB	1	CH <sub>3</sub>				NC(CH <sub>2</sub> ) <sub>4</sub> -	125
214	NSB	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> -	125
215	S,R	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> -	126
216	S,S	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> -	127
217	R,R	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> -	128
218	R,S	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> -	129
219	S,R	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	126
220	S,S	1	CH <sub>3</sub>				H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	127

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Table VI- Compound of formula I by process [a.1]

Cpd No.	Stereo-chemistry	n'	R2	Ar1	Ar2	Z	W	Starting cpd No.
221	R,R	1	CH <sub>3</sub>	phenyl	3,5-bis(trifluoromethyl)phenyl	O	H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	128
222	R,S	1	CH <sub>3</sub>	phenyl	3,5-bis(trifluoromethyl)phenyl	O	H <sub>2</sub> N(CO)CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	129
223	racemic	2	H	phenyl	3,5-bis(trifluoromethyl)phenyl	O	MeO(CO)CH <sub>2</sub> -	130
224	racemic	2	H	phenyl	3,5-bis(trifluoromethyl)phenyl	O	3-(MeO(CO))-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	130
227	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	O	4-quinolyl	86
228	racemic	1	H	phenyl	3,5-bis(trifluoromethyl)phenyl	S	MeO(CO)CH <sub>2</sub> -	131

Table VIa -

Physico-chemical properties of compounds of formula I.				
	I	Stereo-chemistry	Salt	Characteristics
5	134	racemic	2 HCl	- <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.84 (s, 2H), 7.5-7.3 (m, 5H), 4.69 (dd, 2H), 4.44 (t, 1H), 4.04 (m, 2H), 3.95 (dd, 2H), 3.66 (s, 2H), 6.64 (s, 3H), 3.3-3.15 (m, 2H), 3.1-3.0 (m, 6H). - Mass : (LC/MS APCI+): 505 (MH+).
10	137	S	2 HCl .½ H <sub>2</sub> O	- <sup>1</sup> H-NMR (DMSO): 7.90 (s, 1H), 7.87 (s, 2H), 7.55-7.4 (m, 5H), 4.71 dd, 2H), 4.59 (t, 1H), 4.13 (dd, 1H), 4.02 (dd, 1H), 3.88 (s, 2H), 3.5-3.3 (m, 6H), 3.3-3.1 (m, 2H), 1.4 (s, 9H). - Mass : (LC/MS APCI+): 547 (MH+). - [a]D= +14.77° (1% CH <sub>3</sub> OH, 25°C).
15	138	racemic	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.9 (s, 1H), 7.75 (s, 2H), 7.25 (m, 5H), 6.17 (s, 4H), 4.6 (dd, 2H), 4.1-3.75 (m, 2H), 3.1 (m, 4H), 2.95 (m, 2H), 2.65 (m, 4H), 2.32 (t, 2H), 1.81 (m, 2H), 1.13(t, 3H). - Mass : (LC/MS APCI+): 547 (MH+).
20	139	racemic	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.78 (s, 2H), 7.30 (m, 5H), 6.17 (s, 4H), 4.62 (s, 2H), 4.0-3.8 (m, 3H), 3.77 (s, 3H), 3.3-3.1 (m, 4H), 2.97 (t, 2H), 2.8-2.6 (m, 4H), 2.30 (t, 2H), 1.7-1.5 (m, 4H). - Mass : (LC/MS APCI+): 547 (MH+).
25	141	racemic	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.89 (s, 1H), 7.75 (s, 2H), 7.29 (m, 5H), 6.17 (s, 4H), 4.61 (s, 2H), 4.06 (q, 2H), 4.0-3.8 (m, 3H), 3.3-3.1 (m, 4H), 3.01 (t, 2H), 2.8-2.6 (m, 4H), 2.28 (t, 2H), 1.7-1.5 (m, 4H), 1.27 (m, 2H), 1.17 (t, 3H). - Mass : (LC/MS APCI+): 575 (MH+).
30	142	racemic	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.89 (s, 1H), 7.76 (s, 2H), 7.29 (m, 5H), 6.17 (s, 4H), 4.82 (m, 1H), 4.61 (s, 2H), 4.05-3.8 (m, 3H), 3.3-3.1 (m, 4H), 2.94 (t, 2H), 2.8-2.6 (m, 4H), 2.20 (t, 2H), 1.7-1.5 (m, 4H), 1.24 (m, 2H), 1.12 (d, 6H) - Mass : (LC/MS APCI+): 589 (MH+).
35	144	S	2 HCl	- <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.85 (s+s, 3H), 7.5-7.3 (m, 6H), 4.7 (s, 2H), 4.25 (t, 1H), 4.0-3.85 (m, 2H), 3.55 (s, 2H), 3.2-3.1 (m, 6H), 3.05-2.9 (m, 2H). - Mass : (LC/MS APCI+): 490 (MH+). - [α] <sub>D</sub> = +15.43° (1% CH <sub>3</sub> OH, 25°C).
40	145	R	2 HCl	<sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.85 (s+s, 3H),
45				
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55				

Table VIa - (continued)

Physico-chemical properties of compounds of formula I.			
I	Stereo-chemistry	Salt	Characteristics
5			7.5-7.3 (m, 6H), 4.7 (dd, 2H), 4.44 (t, 1H), 4.05 (dd, 1H), 3.95 (dd, 1H), 3.73 (s, 2H), 3.4-3.2 (m, 6H), 3.3-3.0 (m, 2H). - Mass : (EI/DIP): 489 (M+). - $[\alpha]_D = -17.7^\circ$ (1% CH <sub>3</sub> OH, 25°C).
10	147	racemic	2 HCl . 1/2 H <sub>2</sub> O - <sup>1</sup> H-NMR (DMSO): 7.89 (s, 1H), 7.83 (s, 2H), 7.6 (s, 1H), 7.5-7.3 (m, 5H), 7.15 (s, 1H), 4.69 (dd, 2H), 4.44 (t, 1H), 4.15-3.95 (m, 2H), 3.91 (s, 2H), 3.74 (t, 2H), 3.6-3.4 (m, 4H), 3.4-3.2 (m, 4H), 3.2-3.1 (m, 2H). - Mass : (LC/MS ESI +): 534 (MH+).
15	148	S	2 maleate ½ H <sub>2</sub> O - <sup>1</sup> H-NMR (DMSO): 7.88 (s, 1H), 7.74 (s, 2H), 7.3 (m, 5H), 6.18 (s, 4H), 4.60 (s, 2H), 4.0-3.7 (m, 7H), 3.88 (s, 2H), 3.69 (t, 2H), 3.2 (m, 6H), 2.7 (m, 2H). - Mass : (LC/MS APCI+): 534 (MH+). - $[\alpha]_D = +8.27^\circ$ (1% CH <sub>3</sub> OH, 25°C).
20	149	R	2 maleate ½ H <sub>2</sub> O - <sup>1</sup> H-NMR (DMSO): 7.88 (s, 1H), 7.75 (s, 2H), 7.3 (m, 5H), 6.18 (s, 4H), 4.61 (s, 2H), 4.0-3.7 (m, 7H), 3.88 (s, 2H), 3.68 (t, 2H), 3.2 (m, 6H), 2.7 (m, 2H). - Mass : (LC/MS APCI+): 534 (MH+). - $[\alpha]_D = -20^\circ$ (1% CH <sub>3</sub> OH, 25°C).
25	150	racemic	2 maleate - <sup>1</sup> H-NMR (DMSO): 7.97 (s, 1H), 7.87 (s, 2H), 7.35 (m, 5H), 7.15 (s, 1H), 6.75 (s, 1H), 6.14 (s, 4H), 4.69 (s, 2H), 4.05-3.85 (m, 3H), 3.3-3.1 (m, 4H), 3.04 (t, 2H), 2.8-2.6 (m, 4H), 2.04 (t, 2H), 1.7-1.5 (m, 4H), 1.28 (m, 2H). - Mass : (LC/MS APCI): 546 (MH+).
30	151	racemic	2 maleate - <sup>1</sup> H-NMR (DMSO): 7.88 (s, 1H), 7.75 (s, 2H), 7.3 (m, 5H), 6.17 (s, 4H), 4.61 (m, 2H), 4.0-3.8 (m, 3H), 3.1 (m, 4H), 2.95 (m, 2H), 2.7 (m, 4H), 2.5 (m, 2H), 1.85 (m, 2H). - Mass : (LC/MS APCI+): 500 (MH+)
35	152	racemic	2 maleate - <sup>1</sup> H-NMR (DMSO): 7.89 (s, 1H), 7.76 (s, 2H), 7.32 (m, 5H), 6.18 (s, 4H), 4.61 (s, 2H), 4.1-3.8 (m, 5H), 3.3-3.2 (m, 4H), 3.01 (t, 2H), 2.8-2.6 (m, 4H), 2.45 (t, 2H), 1.8-1.5 (m, 4H). - Mass : (LC/MS APCI): 514 (MH+).
40	155	racemic	2 maleate - <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.78 (s, 2H), 7.32 (m, 5H), 6.17 (s, 4H), 4.62 (s, 2H), 4.40 (s,
45			
50			
55			

Table VIa - (continued)

Physico-chemical properties of compounds of formula I.				
	I	Stereo-chemistry	Salt	Characteristics
5				2H), 4.1-3.8 (m, 5H), 3.19 (t, 2H), 3.2-3.1 (m, 4H), 2.96 (t, 2H), 2.8-2.6 (m, 4H). - Mass : (LC/MS APCI): 516 (MH+).
10	156	racemic	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.88 (s, 1H), 7.75 (s, 2H), 7.32 (m, 5H), 6.18 (s, 4H), 4.60 (s, 2H), 4.1-3.8 (m, 3H), 3.3-3.1 (m, 4H), 2.96 (t, 2H), 2.8-2.6 (m, 4H), 2.40 (t, 2H), 1.7-1.5 (m, 4H), 1.27 (m, 2H).
15	157	racemic	2 HCl .½ H <sub>2</sub> O	- Mass : (LC/MS APCI): 528 (MH+) - <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.83 (s, 2H), 7.5-7.3 (m, 5H), 4.68 (dd, 2H), 4.36 (t, 1H), 4.1-3.9 (m, 2H), 3.7 (t, 1H), 3.5-3.3 (m, 4H), 3.3-3.0 (m, 6H). - Mass : (LC/MS APCI+): 477 (MH+).
20	158	S	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.89 (s, 1H), 7.76 (s, 2H), 7.3 (m, 5H), 6.17 (s, 4H), 4.61 (dd, 2H), 4.0-3.75 (m, 3H), 3.65 (t, 2H), 3.48 (m, 2H), 3.45 (m, 2H), 3.18 (m, 6H), 2.7 (m, 2H). - Mass : (LC/MS APCI+): 521 (MH+). - [α] <sub>D</sub> = +9° (1% CH <sub>3</sub> OH, 25°C)
25	159	racemic	1 H <sub>2</sub> O	- <sup>1</sup> H-NMR (DMSO): 7.76 (s, 1H), 7.64 (s, 2H), 7.35-7.15 (m, 5H), 4.55 (s, 2H), 3.9-3.6 (m, 3H), 3.5 (t, 2H), 3.3 (t, 2H), 3.1-2.6 (m, 8H). - Mass : (LC/MS APCI+): 541 (MH+).
30	160	racemic	2 HCl	- <sup>1</sup> H-NMR (DMSO): 7.90 (s, 1H), 7.83 (s, 2H), 7.45-7.35 (m, 5H), 4.68 (m, 2H), 4.40 (t, 1H), 4.2-3.8 (m, 2H), 3.5-3.3 (m, 4H), 3.3-3.0 (m, 6H), 2.67 (t, 2H), 1.97 (t, 2H). - Mass : (LC/MS APCI+): 555 (MH+).
35	161	racemic	3 HCl	- <sup>1</sup> H-NMR (DMSO): 7.95 (s, 1H), 7.89 (s, 2H), 7.6-7.5 (m, 2H), 7.5-7.4 (m, 3H), 4.73 (s, 2H), 4.55 (t, 1H), 4.15 (dd, 1H), 4.05 (dd, 1H), 3.55-3.4 (m, 4H), 3.4-3.25 (m, 6H), 3.25-3.15 (m, 6H), 3.15-3.05 (m, 4H). - Mass : (LC/MS APCI+): 594 (MH+).
40	162	racemic	3 HCl	- <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.5 (m, 2H), 7.4 (m, 3H), 4.7 (dd, 2H), 4.53 (t, 1H), 4.15-3.85 (m, 2H), 3.85 (t, 4H), 3.4-3.15 (m, 8H), 3.05 (m, 2H), 2.95-2.75 (m, 6H). - Mass : (LC/MS APCI+): 546 (MH+).
45	164	S	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.88 (s, 2H),

Table VIa - (continued)

Physico-chemical properties of compounds of formula I.			
I	Stereo-chemistry	Salt	Characteristics
5			7.36 (m, 5H), 6.14 (s, 4H), 4.69 (s, 2H), 4.1-3.8 (m, 3H), 4.03 (q, 4H), 3.4-3.1 (m, 8H), 2.8-2.6 (m, 2H), 2.20 (m, 2H), 1.24 (t, 3H). - Mass : (LC/MS APCI+): 597 (MH+). - $[\alpha]_D = +9.32^\circ$ (1% CH <sub>3</sub> OH, 25°C).
10			
15			
20	165	racemic	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.99 (d, 1H), 7.91 (s, 1H), 7.83 (s, 2H), 7.65-7.5 (m, 3H), 7.4-7.3 (m, 5H), 4.68 (s, 2H), 4.43 (s, 2H), 4.25 (q, 2H), 4.1-3.8 (m, 3H), 3.3-3.2 (m, 4H), 3.2-3.05 (m, 2H), 3.05-2.9 (m, 2H), 1.27 (t, 3H). - Mass : (LC/MS APCI+): 595 (MH+).
25			
30	168	S, rac.	2 HCl .1 H <sub>2</sub> O - <sup>1</sup> H-NMR (DMSO): 7.89 (s, 1H), 7.82 (s, 2H), 7.5-7.2 (m, 5H), 4.75-4.6 (dd, 2H), 4.66 (s, 1H), 4.6-4.4 (m, 1H), 4.2-3.9 (m, 2H) 3.58 (s, 3H), 3.3-3.15 (m, 2H), 3.1-2.95 (m, 2H), 2.77 (m, 4H). - Mass : (LC/MS APCI+): 581 (MH+). - $[\alpha]_D = +16.47^\circ$ (1% CH <sub>3</sub> OH, 25°C).
35			
40	170	racemic	3 HCl .½ H <sub>2</sub> O - <sup>1</sup> H-NMR (DMSO): 8.68 (d, 1H), 8.2 (t, 1H), 7.95 (s, 1H), 7.9 (s, 2H), 7.76 (d, 1H), 7.7 (t, 1H), 7.6 (m, 2H), 7.45 (m, 3H), 4.73 (s, 2H), 4.67 (t, 1H), 4.26 (s, 2H), 4.2 (dd, 1H), 4.05 (dd, 1H), 3.5-3.4 (m, 2H), 3.2 (m, 6H). - Mass : (EI/DIP): 523 (M+).
45			
50	171	racemic	- - <sup>1</sup> H-NMR (DMSO): 7.9 (d, 1H), 7.75 (s, 1H), 7.64 (s, 2H), 7.5-7.1 (m, 8H), 4.57 (s, 2H), 4.3-4.1 (m, 2H), 4.0-3.7 (m, 6H), 3.65 (t, 1H), 3.14 (t, 2H), 2.7-2.5 (m, 2H), 2.5-2.3 (m, 2H). - Mass : (LC/MS APCI+): 606 (MH+).
55	173	S	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.85 (s, 2H), 7.5-7.3 (m, 5H), 6.82 (s, 2H), 4.69 (s, 2H), 4.41 (t, 1H), 4.22 (s, 2H), 4.05 (dd, 1H), 3.95 (dd, 1H), 3.76 (s, 6H), 3.64 (s, 3H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : (EI/DIP): 612 (M+). - $[\alpha]_D = +19.63^\circ$ (1% CH <sub>3</sub> OH, 25°C).
	174	R	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.5-7.3 (m, 5H), 6.81 (s, 2H), 4.68 (s, 2H), 4.33 (t, 1H), 4.19 (s, 2H), 4.05 (dd, 1H), 3.95 (dd, 1H), 3.76 (s, 6H), 3.64 (s, 3H), 3.4-3.15 (m, 6H), 3.1-2.95 (m, 2H). - Mass : (EI/DIP): 612 (M+). - $[\alpha]_D = -20.09^\circ$ (1% CH <sub>3</sub> OH, 25°C).

Table VIa - (continued)

Physico-chemical properties of compounds of formula I.			
I	Stereo-chemistry	Salt	Characteristics
5	176	NSA	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.83 (s, 2H), 7.39 (m, 5H), 6.6 (s, 2H), 4.67 (s, 2H), 4.4 (s, 2H), 4.21 (t, 1H), 4.05-3.85 (m, 2H), 3.87 (s, 6H), 3.85 (m, 2H), 3.7 (s, 3H), 3.4-3.25 (m, 6H), 3.2-2.9 (m, 4H). - Mass : (EI/DIP): 656 (M+). - [α] <sub>D</sub> = +12,61° (1% CH <sub>3</sub> OH, 25°C).
10	177	NSB	2 HCl - <sup>1</sup> H-NMR (DMSO): 7.9 (s, 1H), 7.81 (s, 2H), 7.38 (m, 5H), 6.6 (s, 2H), 4.66 (s, 2H), 4.39 (s, 2H), 4.21 (t, 1H), 4.05-3.85 (m, 2H), 3.92 (s, 6H), 3.9 (m, 2H), 3.69 (s, 3H), 3.4-3.25 (m, 6H), 3.2-2.9 (m, 4H). - Mass : (EI/DIP): 656 (M+). - [α] <sub>D</sub> = -17,73° (1% CH <sub>3</sub> OH, 25°C).
15	182	NSA	2 maleate - <sup>1</sup> H-NMR (DMSO): 7.99 (s, 1H), 7.89 (s, 2H), 7.49 (s, 1H), 7.39 (m, 3H), 6.17 (s, 4H), 4.70 (s, 2H), 4.05 (m, 1H), 3.95 (m, 2H), 3.71 (s, 2H), 3.68 (s, 3H), 3.1-2.9 (m, 6H), 2.8 (m, 2H). - Mass : (LC/MS APCI): 539 (MH+).
20	188	racemic	2 maleate - <sup>1</sup> H-NMR (DMSO): 8.00 (s, 1H), 7.85 (s, 2H), 7.4 (m, 1H), 7.26 (m, 2H), 6.18 (s, 4H), 4.69 (dd, 2H), 4.24 (t, 1H), 4.0-3.9 (m, 2H), 3.89 (s, 2H), 3.70 (s, 3H), 3.0 (m, 4H), 2.7 (m, 4H). - Mass : (LC/MS APCI+): 541 (MH+).
25	191	racemic	2 HCl - <sup>1</sup> H-NMR (DMSO): 8.21 (d, 1H), 7.85 (m, 2H), 7.81 (s, 1H), 7.75-7.65 (m, 3H), 7.5-7.4 (m, 3H), 4.98 (m, 1H), 4.62 (s, 2H), 4.1-3.9 (m, 2H), 3.67 (s, 2H), 3.3-3.15 (m, 6H), 3.15-2.95 (m, 2H). - Mass : (LC/MS APCI+): 540 (MH+).
30	192	racemic	- - <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.95 (s, 2H), 7.41 (dd, 1H), 7.0-6.9 (m, 2H), 4.72 (s, 2H), 4.09 (t, 1H), 3.91 (dd, 1H), 3.82 (dd, 1H), 3.59 (s, 3H), 3.26 (s, 2H), 2.6-2.4 (m, 8H). - Mass : (LC/MS APCI+): 511 (MH+).
35	193	racemic	- - <sup>1</sup> H-NMR (DMSO): 7.96 (s, 1H), 7.92 (s, 2H), 7.46 (m, 1H), 7.31 (d, 1H), 7.05 (dd, 1H), 4.69 (s, 2H), 4.0-3.75 (m, 3H), 3.59 (s, 3H), 3.25 (s, 2H), 2.6-2.35 (m, 8H). - Mass : (LC/MS APCI+): 511 (MH+)
40	194	racemic	- <sup>1</sup> H-NMR (DMSO): 7.97 (s, 1H), 7.93 (s, 2H), 7.57 (d, 1H), 6.41 (m, 1H), 6.29 (dd, 1H), 4.7 (dd,
45			
50			
55			

Table VIa - (continued)

Physico-chemical properties of compounds of formula I.			
I	Stereo-chemistry	Salt	Characteristics
200	racemic	-	2H), 4.0-3.8 (m, 3H), 3.58 (s, 3H), 3.26 (s, 2H), 2.5-2.3 (m, 8H). - Mass : (LC/MS APCI+): 495 (MH+)
208	racemic	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.35-7.2 (m, 5H), 7.0-6.85 (s+s, 2H), 6.5 (s, 2H), 4.38 (s, 2H), 3.99 (q, 1H), 3.8-3.3 (m, 2H), 3.71 (s, 6H), 3.64 (s, 3H), 2.7 (s, 2H), 2.5-2.4 (m, 8H). - Mass : (LC/MS APCI+): 444 (MH+).
219	S,R	2 maleate	- <sup>1</sup> H-NMR (DMSO): 7.86 (s, 1H), 7.62 (s, 1H), 7.47 (s, 1H), 7.48 (m, 5H), 6.15 (s, 4H), 4.51 (s, 2H), 4.36 (m, 1H), 3.94 (m, 2H), 3.66 (s, 3H), 3.55 (s, 2H), 3.0-2.8 (m, 8H). - Mass : (LC/MS APCI): 573/575 (MH+). - $[\alpha]_D = +27$ (1% CH <sub>3</sub> OH, 25°C).

## 1.4.2. Preparation of compounds of formula I according to process (a.2).

**[0070]** In a round-bottomed flask fitted with a reflux condenser and a thermometer 2.48 g (4 mmoles) of 5-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-pentanoic acid ethyl ester (compound 140 prepared at example 1.4.1 above), 45 ml of ethyl alcohol, 4 ml of water, and 6.6 ml of a 1N solution of sodium hydroxide in water were introduced. The mixture was stirred at room temperature for 22 hours, and 6.6 ml of a 1N solution of hydrochloric acid in water was added. The volatile substances were removed under reduced pressure, water and methylene chloride were added, the aqueous layer was extracted with methylene chloride, and the combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 35 ml of methylene chloride, 3.96 ml of a 1.96 N solution of hydrochloric acid in diethyl ether were added, and the volatile substances were removed under reduced pressure. The residue was recrystallized from acetonitrile, affording 1.6 g of 5-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-pentanoic acid (compound 233) as a solid. Yield: 61%.

**[0071]** The compounds listed in Table VII were obtained by the same method. Physico-chemical properties of the compounds of formula I prepared according to this method are given in Table VIIa below. When the compounds of formula I are in the form of non toxic pharmaceutically acceptable salts, they are obtained by the general methods given above.

Table VII -

Preparation of compounds of formula I by process (a.2)				
Cpd No.	W	Stereo-chemistry	Hydrolysis	Starting Cpd No
229	HOOC-CH <sub>2</sub> -	racemic	KOH, room temp., 1 night	134 or 135
230	HOOC-CH <sub>2</sub> -	S	KOH (3 eq), room temp., 4h or HCl 1N, 100°C, 11h	144

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Table VII - (continued)

Preparation of compounds of formula I by process (a.2)					
	Cpd No.	W	Stereo-chemistry	Hydrolysis	Starting Cpd No
5	231	HOOC-CH <sub>2</sub> -	R	KOH (2.5 eq), room temp., 1 night, or NaOH, EtOH, H <sub>2</sub> O	145
10	232	HOOC-(CH <sub>2</sub> ) <sub>3</sub> -	racemic	KOH (3 eq), EtOH, reflux, 1h	138
15	233	HOOC-(CH <sub>2</sub> ) <sub>4</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	140
20	234	HOOC-(CH <sub>2</sub> ) <sub>5</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	141 or 150
25	235	HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	racemic	HCl 1N, 50°C, 1 night	147
30	236	HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	S	HCl 6N, 50°C, 3h30	148
35	237	HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	R	HCl 6N, 50°C 1 night	149
40	238	HOOC-CH <sub>2</sub> -NH-C(O)-CH <sub>2</sub> -	S	KOH (2.5 eq), EtOH, 0-50C, 2h	290
45	239	(HO) <sub>2</sub> (PO)(CH <sub>2</sub> ) <sub>2</sub> -	racemic	HCl 6N, 100°C, 4 days	163
50	240	(HO)(EtO)(PO)(CH <sub>2</sub> ) <sub>2</sub> -	S	KOH (4 eq), EtOH, reflux, 24h	164
55	241	2-(HOOC)-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room temp., 48h	165
	242	3-(HOOC)-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	racemic	KOH (6 eq), MeOH, reflux, 4 days	166
	243	4-(HOOC)-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	S	KOH (3 eq), MeOH, reflux, 1 night	167
	244	C <sub>6</sub> H <sub>5</sub> CH(COOH)-	S, rac	HCl 6N, CH <sub>3</sub> COOH, 50°C, 7 days	168
	245	HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	178
	246	HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	179
	247	HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	180
	248	HOOC-CH <sub>2</sub> -	NSA	KOH (10 eq), EtOH, reflux, 1h	182
	249	HOOC-CH <sub>2</sub> -	NSB	KOH (10 eq), EtOH, reflux, 6h	183
	250	HOOC-CH <sub>2</sub> -	racemic	KOH, room temp., 48h	184

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Table VII - (continued)

Preparation of compounds of formula I by process (a.2)					
	Cpd No.	W	Stereo-chemistry	Hydrolysis	Starting Cpd No
5	251	HOOC-CH <sub>2</sub> -	NSA	NaOH, EtOH, H <sub>2</sub> O	186
	252	HOOC-CH <sub>2</sub> -	NSB	NaOH, EtOH, H <sub>2</sub> O	187
10	253	HOOC-CH <sub>2</sub> -	racemic	KOH (3 eq), MeOH, reflux, 1h30	188
	254	HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	189
15	255	HOOC-CH <sub>2</sub> - HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, KOH (2.5 eq), MeOH, room t°, 48h	190
	256	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room t°, 24h	192
20	257	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room t°, 24h	193
	258	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room t°, 24h	194
25	259	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room t°, 48h	195
	260	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room t°, 48h	196
30	261	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, reflux, 2h	197
	262	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, reflux, 3h	198
35	263	HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, room temp., 24h	199
	264	HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	201
40	265	HOOC-CH <sub>2</sub> -	racemic	HCl 3N, 50°C, 55h	202
	266	HOOC-CH <sub>2</sub> -	S	NaOH, EtOH, H <sub>2</sub> O	203
45	267	HOOC-CH <sub>2</sub> -	R	NaOH, EtOH, H <sub>2</sub> O	204
	268	HOOC-CH <sub>2</sub> -	racemic	HCl 3N, 50°C, 24h	205
50	269	HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	206

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Table VII - (continued)

Preparation of compounds of formula I by process (a.2)				
Cpd No.	W	Stereo-chemistry	Hydrolysis	Starting Cpd No
5	270 HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	207
10	271 HOOC-CH <sub>2</sub> -	racemic	KOH (3 eq), MeOH, reflux, 4h	208
15	272 HOOC-CH <sub>2</sub> -	racemic	NaOH, EtOH, H <sub>2</sub> O	209
20	273 HOOC-CH <sub>2</sub> -	NSA	KOH (3 eq), room temp., 4h	210
25	274 HOOC-CH <sub>2</sub> -	NSB	KOH (3 eq), room temp., 6h	211
30	275 HOOC-CH <sub>2</sub> -	S,R	HCl 10%	215
35	276 HOOC-CH <sub>2</sub> -	S,S	HCl 10%	216
40	277 HOOC-CH <sub>2</sub> -	R,R	HCl 10%	217
45	278 HOOC-CH <sub>2</sub> -	R,S	HCl 10%	218
50	279 HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	S,R	HCl 6N, 50°C, 2h	219
55	280 HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	S,S	HCl 6N, 50°C, 2h	220
60	281 HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	R,R	HCl 6N, 50°C, 20h	221
65	282 HOOC-CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	R,S	HCl 6N, 50°C, 20h	222
70	283 HOOC-CH <sub>2</sub> -	racemic	KOH (2.5 eq), MeOH, reflux, 4h	223
75	284 3-(HOOC)-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	NSA	KOH (2.5 eq), MeOH, reflux, 4h	225
80	285 3-(HOOC)-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	NSB	KOH (3 eq), MeOH, reflux, 3h	226
85	286 HOOC-CH <sub>2</sub> -	racemic	HCl 6N, 50°C, 48h	228

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Table VIIa – Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereochemistry	Analysis	
			2 HCl	
229		racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.97 (s, 1H), 7.94 (s, 2H), 7.62 (m, 2H), 7.4 (m, 2H), 4.74 (s, 2H), 4.6 (m, 1H), 4.35 (dd, 1H), 3.95 (dd, 1H), 3.95 (s, 2H), 3.5-3.3 (m, 6H), 3.3-3.1 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 491 (MH<math>^+</math>).</p>	
230	2 HCl . 1/2 $\text{H}_2\text{O}$	S	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.91 (s, 1H), 7.83 (s, 2H), 7.4 (m, 5H), 4.67 (s, 2H), 4.29 (t, 1H), 4.1-3.9 (m, 2H), 3.68 (s, 2H), 3.2-3.05 (m, 6H), 3.05-2.9 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 491 (MH<math>^+</math>).</p> <p>- <math>[\alpha]_D = +12.6</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p>	
	2 maleate		<p>- <math>^1\text{H-NMR}</math> (DMSO): 8.0 (s, 1H), 7.9 (s, 2H), 7.5-7.3 (m, 5H), 6.17 (s, 4H) 4.7 (s, 2H), 4.1-3.85 (m, 3H), 3.79 (s, 2H), 3.2-3.1 (m, 4H), 3.0-2.85 (m, 2H), 2.85-2.7 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 491 (MH<math>^+</math>).</p> <p>- <math>[\alpha]_D = +5.8</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p>	
231	2 HCl . 1 $\text{H}_2\text{O}$	R	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.98 (s, 1H), 7.93 (s, 2H), 7.6 (m, 2H), 7.4 (m, 3H), 4.74 (s, 2H), 4.6-4.4 (m, 1H), 4.25 (m, 1H), 3.95 (dd, 1H), 3.91 (s, 2H), 3.5-3.3 (m, 6H), 3.2-2.9 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 491 (MH<math>^+</math>).</p> <p>- <math>[\alpha]_D = -17.8</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p>	
	2 maleate		<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.98 (s, 1H), 7.89 (s, 2H), 7.39 (m, 5H), 6.15 (s, 4H), 4.70 (s, 2H), 4.1-3.9 (m, 3H), 3.76 (s, 2H), 3.2 (m, 4H), 3.0-2.8 (m, 4H).</p> <p>- Mass : (LC/MS APCI+): 491 (MH<math>^+</math>).</p> <p>- <math>[\alpha]_D = -13.51</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p>	
232	2 maleate	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.97 (s, 1H), 7.87 (s, 2H), 7.34 (m, 5H), 6.14 (s, 4H), 4.69 (s, 2H), 4.1-3.8 (m, 3H), 3.4-3.2 (m, 4H), 3.05 (t, 2H), 2.8-2.6 (m, 4H), 2.30 (t, 2H), 1.85 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 519 (MH<math>^+</math>).</p> <p>- Mass : (LC/MS APCI-): 517 (M-H).</p>	
233	2 HCl	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.98 (s, 1H), 7.96 (s, 2H), 7.65 (m, 2H), 7.45 (m, 3H), 4.74 (s, 2H), 4.65 (m, 1H), 4.3 (m, 1H), 4.0 (dd, 1H), 3.7-3.0 (m, 10H), 2.25 (t, 2H), 1.75-1.6 (m, 2H), 1.6-1.4 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 533 (MH<math>^+</math>).</p>	
234	3/2 maleate	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.88 (s, 1H), 7.75 (s, 2H), 7.30 (m, 5H), 6.19 (s, 4H), 4.61 (s, 2H), 4.1-3.8 (m, 3H), 3.3-3.1 (m, 4H), 3.05 (t, 2H), 2.8-2.6 (m, 4H), 2.22 (t, 2H), 1.7-1.5 (m, 4H), 1.27 (m, 2H).</p> <p>- Mass : (LC/MS APCI+): 547 (MH<math>^+</math>).</p>	

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Table VIIa – Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereochemistry	Analysis
235	2 maleate	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.97 (s, 1H), 7.87 (s, 2H), 7.4-7.3 (m, 5H), 6.11 (s, 4H), 4.69 (s, 2H), 4.07 (s, 2H), 3.95-3.8 (m, 3H), 3.85 (t, 2H), 3.77 (t, 2H), 3.25 (m, 6H), 2.7 (m, 2H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 535 (<math>\text{MH}^+</math>).</p>
	2 HCl		<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.9 (s, 1H), 7.85 (s, 2H), 7.5-7.3 (m, 5H), 4.7 (dd, 2H), 4.4 (t, 1H), 4.05 (s, 2H), 4.1-3.9 (m, 2H), 3.75 (t, 2H), 3.6-3.4 (m, 4H), 3.4-3.2 (m, 4H), 3.2-3.0 (m, 2H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 535 (<math>\text{MH}^+</math>).</p>
236	2 HCl	S	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.90 (s, 1H), 7.82 (s, 2H), 7.5-7.3 (m, 5H), 4.68 (m, 2H), 4.36 (m, 1H), 4.2-3.9 (m, 4H), 3.75 (t, 2H), 3.5-3.0 (m, 10H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 535 (<math>\text{MH}^+</math>).</p>
	2 maleate		<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.89 (s, 1H), 7.76 (s, 2H), 7.30 (m, 5H), 6.18 (s, 4H), 4.61 (s, 2H), 4.05 (s, 2H), 4.1-3.8 (m, 3H), 3.78 (t, 2H), 3.4-3.2 (m, 6H), 2.9-2.7 (m, 4H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 535 (<math>\text{MH}^+</math>).</p>
237	2 HCl	R	<p>- <math>[\alpha]_D = 9.87</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p> <p>- <math>^1\text{H-NMR}</math> (DMSO): 7.90 (s, 1H), 7.79 (s, 2H), 7.3 (m, 5H), 4.64 (m, 2H), 4.2-3.9 (m, 5H), 3.73 (t, 2H), 3.4-2.8 (m, 10H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 535 (<math>\text{MH}^+</math>).</p>
	2 maleate		<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.97 (s, 1H), 7.87 (s, 2H), 7.35 (m, 5H), 6.14 (s, 4H), 4.69 (s, 2H), 4.07 (s, 2H), 4.0-3.8 (m, 5H), 3.4-3.2 (m, 4H), 2.9-2.7 (m, 4H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 535 (<math>\text{MH}^+</math>).</p>
238	-	S	<p>- <math>[\alpha]_D = -12.82</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p> <p>- <math>^1\text{H-NMR}</math> (DMSO): 7.86 (s, 1H), 7.75 (s, 2H), 7.35-7.15 (m, 5H), 4.6 (s, 2H), 3.8 (m, 2H), 3.65 (t, 1H), 3.57 (s, 2H), 2.95 (s, 2H), 2.55-2.45 (m, 8H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 548 (<math>\text{MH}^+</math>).</p>
	2 HCl		<p>- <math>[\alpha]_D = +17.2</math> (1% <math>\text{CH}_3\text{OH}</math>, 25°C).</p>
239	2 HCl	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.92 (s, 1H), 7.84 (s, 2H), 7.40 (m, 5H), 4.68 (s, 2H), 4.32 (t, 1H), 4.1-3.8 (m, 2H), 3.4 (m, 4H), 3.25 (m, 4H), 3.1 (m, 2H), 2.1-1.9 (m, 2H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 540 (<math>\text{MH}^+</math>).</p>
240	2 maleate · 1 $\text{H}_2\text{O}$	S	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.97 (s, 1H), 7.86 (s, 2H), 7.34 (m, 5H), 6.12 (s, 4H), 4.68 (s, 2H), 4.1-3.8 (m, 5H), 3.3-3.1 (m, 6H), 2.9-2.6 (m, 4H), 2.1-1.9 (m, 2H), 1.19 (t, 3H).</p> <p>- Mass : <math>(\text{LC/MS APCI}^+)</math>: 569 (<math>\text{MH}^+</math>).</p>

Table VIIa – Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereochemistry	Analysis
241	2 HCl . 1 H <sub>2</sub> O	racemic	- <sup>1</sup> H-NMR (DMSO): 8.01 (d, 1H), 7.90 (s, 1H), 7.80 (s, 2H), 7.65-7.5 (m, 3H), 7.4-7.3 (m, 5H), 4.66 (s, 2H), 4.46 (s, 2H), 4.27 (t, 1H), 4.15-3.9 (m, 2H), 3.35 (m, 4H), 3.2-3.05 (m, 2H), 3.05-2.9 (m, 2H). - Mass : [LC/MS APCI+]: 567 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 8.17 (s, 1H), 7.94 (d, 1H), 7.7-7.55 (m, 4H), 7.5-7.3 (m, 6H), 4.65 (dd, 2H), 4.3 (m, 1H), 4.15-3.85 (m, 4H), 3.5-3.1 (m, 8H). - Mass : [LC/MS APCI+]: 567 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.95 (d, 2H), 7.88 (s, 2H), 7.59 (d, 2H), 7.38 (m, 5H), 6.17 (s, 2H), 4.69 (s, 2H), 4.2 (s, 2H), 4.05 (m, 2H), 3.9 (m, 1H), 3.2-3.0 (m, 8H). - Mass : [LC/MS APCI+]: 567 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 18 (1% CH <sub>3</sub> OH)
242	2 HCl . 1/2 H <sub>2</sub> O	racemic	- <sup>1</sup> H-NMR (DMSO): 7.87 (s, 1H), 7.75 (s, 2H), 7.4-7.15 (m, 10H), 4.59 (m, 2H), 4.22 (s, 1H), 3.8-3.6 (m, 3H), 3.05-2.9 (m, 4H), 2.8-2.5 (m, 4H). - Mass : [LC/MS APCI+]: 567 (MH <sup>+</sup> ). - [α] <sub>D</sub> = +10.14 (1% CH <sub>3</sub> OH, 25°C).
243	2 maleate . 1/2 H <sub>2</sub> O	S	- <sup>1</sup> H-NMR (DMSO): 8.0 (s, 1H), 7.85 (s, 2H), 7.25-7.15 (m, 4H), 4.85 (dd, 2H), 3.95 (dd, 1H), 3.85 (dd, 1H), 3.60 (t, 1H), 3.1 (s, 2H), 2.7-2.4 (m, 8H), 2.3 (s, 3H). - Mass : [LC/MS APCI+]: 505 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 8.03 (s, 1H), 7.92 (s, 2H), 7.3-7.2 (m, 4H), 6.14 (s, 4H), 4.71 (s, 2H), 3.99 (m, 1H), 3.8 (m, 2H), 3.76 (s, 2H), 3.3-3.0 (m, 4H), 2.88 (m, 1H), 1.20 (d, 6H). - Mass : [LC/MS APCI+]: 533 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.42 (d, 2H), 6.96 (d, 2H), 4.7 (dd, 2H), 4.47 (t, 1H), 4.1-3.9 (m, 2H), 3.77 (s, 2H), 3.73 (s, 3H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : [LC/MS APCI+]: 521 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.87 (s, 2H), 7.45 (s, 1H), 7.35 (m, 3H), 6.15 (s, 4H), 4.69 (s, 2H), 3.91 (m, 3H), 3.85 (s, 2H), 3.2 (m, 4H), 2.9-2.7 (m, 4H). - Mass : [LC/MS APCI+]: 525/527 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 8.2 (1% CH <sub>3</sub> OH).
244	-	S,rac.	- <sup>1</sup> H-NMR (DMSO): 7.87 (s, 1H), 7.75 (s, 2H), 7.4-7.15 (m, 10H), 4.59 (m, 2H), 4.22 (s, 1H), 3.8-3.6 (m, 3H), 3.05-2.9 (m, 4H), 2.8-2.5 (m, 4H). - Mass : [LC/MS APCI+]: 567 (MH <sup>+</sup> ). - [α] <sub>D</sub> = +10.14 (1% CH <sub>3</sub> OH, 25°C).
245	1 H <sub>2</sub> O	racemic	- <sup>1</sup> H-NMR (DMSO): 8.0 (s, 1H), 7.85 (s, 2H), 7.25-7.15 (m, 4H), 4.85 (dd, 2H), 3.95 (dd, 1H), 3.85 (dd, 1H), 3.60 (t, 1H), 3.1 (s, 2H), 2.7-2.4 (m, 8H), 2.3 (s, 3H). - Mass : [LC/MS APCI+]: 505 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 8.03 (s, 1H), 7.92 (s, 2H), 7.3-7.2 (m, 4H), 6.14 (s, 4H), 4.71 (s, 2H), 3.99 (m, 1H), 3.8 (m, 2H), 3.76 (s, 2H), 3.3-3.0 (m, 4H), 2.88 (m, 1H), 1.20 (d, 6H). - Mass : [LC/MS APCI+]: 533 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.42 (d, 2H), 6.96 (d, 2H), 4.7 (dd, 2H), 4.47 (t, 1H), 4.1-3.9 (m, 2H), 3.77 (s, 2H), 3.73 (s, 3H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : [LC/MS APCI+]: 521 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.87 (s, 2H), 7.45 (s, 1H), 7.35 (m, 3H), 6.15 (s, 4H), 4.69 (s, 2H), 3.89 (m, 3H), 3.84 (s, 2H), 3.2 (m, 4H), 2.9-2.7 (m, 4H). - Mass : [LC/MS APCI+]: 525/527 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 8.2 (1% CH <sub>3</sub> OH).
246	2 maleate	racemic	- <sup>1</sup> H-NMR (DMSO): 8.03 (s, 1H), 7.92 (s, 2H), 7.3-7.2 (m, 4H), 6.14 (s, 4H), 4.71 (s, 2H), 3.99 (m, 1H), 3.8 (m, 2H), 3.76 (s, 2H), 3.3-3.0 (m, 4H), 2.88 (m, 1H), 1.20 (d, 6H). - Mass : [LC/MS APCI+]: 533 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 8.03 (s, 1H), 7.92 (s, 2H), 7.3-7.2 (m, 4H), 6.14 (s, 4H), 4.71 (s, 2H), 3.99 (m, 1H), 3.8 (m, 2H), 3.76 (s, 2H), 3.3-3.0 (m, 4H), 2.88 (m, 1H), 1.20 (d, 6H). - Mass : [LC/MS APCI+]: 533 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.42 (d, 2H), 6.96 (d, 2H), 4.7 (dd, 2H), 4.47 (t, 1H), 4.1-3.9 (m, 2H), 3.77 (s, 2H), 3.73 (s, 3H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : [LC/MS APCI+]: 521 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.87 (s, 2H), 7.45 (s, 1H), 7.35 (m, 3H), 6.15 (s, 4H), 4.69 (s, 2H), 3.91 (m, 3H), 3.85 (s, 2H), 3.2 (m, 4H), 2.9-2.7 (m, 4H). - Mass : [LC/MS APCI+]: 525/527 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 8.2 (1% CH <sub>3</sub> OH).
247	2 HCl . 3/2 H <sub>2</sub> O	racemic	- <sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.42 (d, 2H), 6.96 (d, 2H), 4.7 (dd, 2H), 4.47 (t, 1H), 4.1-3.9 (m, 2H), 3.77 (s, 2H), 3.73 (s, 3H), 3.4-3.2 (m, 6H), 3.2-3.05 (m, 2H). - Mass : [LC/MS APCI+]: 521 (MH <sup>+</sup> ). - <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.87 (s, 2H), 7.45 (s, 1H), 7.35 (m, 3H), 6.15 (s, 4H), 4.69 (s, 2H), 3.91 (m, 3H), 3.85 (s, 2H), 3.2 (m, 4H), 2.9-2.7 (m, 4H). - Mass : [LC/MS APCI+]: 525/527 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 8.2 (1% CH <sub>3</sub> OH).
248	2 maleate	NSA	- <sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.87 (s, 2H), 7.45 (s, 1H), 7.35 (m, 3H), 6.15 (s, 4H), 4.69 (s, 2H), 3.89 (m, 3H), 3.84 (s, 2H), 3.2 (m, 4H), 2.9-2.7 (m, 4H). - Mass : [LC/MS APCI+]: 525/527 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 8.2 (1% CH <sub>3</sub> OH).
249	2 maleate	NSB	- <sup>1</sup> H-NMR (DMSO): 7.99 (s, 1H), 7.87 (s, 2H), 7.46 (s, 1H), 7.37 (m, 3H), 6.14 (s, 4H), 4.69 (s, 2H), 3.89 (m, 3H), 3.84 (s, 2H), 3.2 (m, 4H), 2.9-2.7 (m, 4H). - Mass : [LC/MS APCI+]: 525/527 (MH <sup>+</sup> ). - [α] <sub>D</sub> = 8.2 (1% CH <sub>3</sub> OH).

Table VIIa – Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereochemistry	Analysis
250	2 HCl	racemic	- $^1\text{H-NMR}$ (DMSO): 7.9 (s, 1H), 7.76 (s, 2H), 7.54 (d, 2H), 7.36 (d, 2H), 4.65 (dd, 2H), 4.16 (t, 1H), 4.05-3.85 (m, 2H), 3.82 (s, 2H), 3.3-3.15 (m, 4H), 3.15-3.0 (m, 2H), 3.0-2.8 (m, 2H). - Mass : (LC/MS APCI+): 569/571 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 7.81 (s, 1H), 7.62 (s, 2H), 7.45 (m, 2H), 7.25 (d, 1H), 4.55 (s, 2H), 3.9-3.6 (m, 3H), 3.05 (s, 2H), 2.65-2.35 (m, 8H). - Mass : (LC/MS APCI+): 559/561/563 (MH $^+$ ). - $[\alpha]_D = +6.65$ (1% CH <sub>3</sub> OH, 25°C).
251	1 H <sub>2</sub> O	NSA	- $^1\text{H-NMR}$ (DMSO): 7.85 (s, 1H), 7.65 (s, 2H), 7.45 (m, 2H), 7.27 (d, 1H), 4.58 (s, 2H), 3.83 (m, 2H), 3.65 (t, 1H), 3.06 (s, 2H), 2.6-2.35 (m, 8H). - Mass : (LC/MS APCI+): 559/561/563 (MH $^+$ ). - $[\alpha]_D = -8.91$ (1% CH <sub>3</sub> OH, 25°C).
252	1 H <sub>2</sub> O	NSB	- $^1\text{H-NMR}$ (DMSO): 7.99 (s, 1H), 7.85 (s, 2H), 7.4 (m, 2H), 7.24 (m, 1H), 6.16 (s, 4H), 4.70 (dd, 2H), 4.22 (t, 1H), 4.0-3.9 (m, 2H), 3.98 (s, 2H), 3.22 (m, 4H), 2.75 (m, 4H). - Mass : (LC/MS APCI+): 527 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 7.94 (s, 1H), 7.77 (s, 2H), 7.28 (dd, 2H), 4.64 (s, 2H), 3.81 (d, 2H), 3.65 (t, 1H), 3.08 (s, 2H), 2.6-2.35 (m, 8H). - Mass : (LC/MS APCI+): 545 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 8.4 (s, 1H), 8.22 (dd, 2H), 7.98 (d, 1H), 7.85 (s, 2H), 7.7 (t, 1H), 4.71 (s, 2H), 4.4 (m, 1H), 4.1-3.9 (m, 2H), 4.04 (s, 2H), 3.5-2.9 (m, 8H). - Mass : (LC/MS APCI+): 536 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 7.91 (s, 1H), 7.86 (s, 2H), 7.38 (m, 1H), 6.98 (d, 1H), 4.65 (s, 2H), 4.11 (t, 1H), 3.9-3.75 (m, 2H), 3.25 (s, 2H), 3.1-2.9 (m, 4H), 2.7-2.55 (m, 4H). - Mass : (LC/MS APCI+): 497 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 7.89 (s, 1H), 7.81 (s, 2H), 7.43 (m, 1H), 7.32 (d, 1H), 7.04 (dd, 1H), 4.63 (s, 2H), 4.0-3.75 (m, 3H), 3.33 (s, 2H), 3.2-3.0 (m, 4H), 2.7-2.55 (m, 4H). - Mass : (LC/MS APCI+): 497 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 7.97 (s, 1H), 7.93 (s, 2H), 7.58 (d, 1H), 6.42 (m, 1H), 6.32 (dd, 1H), 4.71 (dd, 2H), 4.0-3.8 (m, 3H), 3.2 (s, 2H), 2.7-2.55 (m, 4H), 2.55-2.4 (m, 4H). - Mass : (LC/MS APCI+): 481 (MH $^+$ ). - $^1\text{H-NMR}$ (DMSO): 7.87 (s, 3H), 7.85-7.75 (m, 1H), 7.72 (m, 3H), 6.65 (m, 3H), 4.68 (s, 2H), 4.2 (t, 1H), 3.9-3.75 (m, 2H), 3.4 (s, 2H), 3.2-3.0 (m, 4H), 2.85-2.7 (m, 4H). - Mass : (LC/MS APCI+): 547 (MH $^+$ ).
253	2 maleate	racemic	
254	1/2 H <sub>2</sub> O	racemic	
255	2 HCl	racemic	
256	-	racemic	
257	-	racemic	
258	-	racemic	
259	-	racemic	

Table VIIa – Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereochemistry	Analysis
260	-	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.94 (s, 3H), 7.58 (dd, 1H), 7.49 (d, 1H), 7.3-7.15 (m, 3H), 4.74 (dd, 2H), 4.12 (t, 1H), 3.99 (d, 2H), 3.07 (s, 2H), 2.75-2.5 (m, 8H).</p> <p>- Mass : [LC/MS APCI+]: 531 (<math>\text{MH}^+</math>).</p>
261	-	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.35 (s, 5H), 6.86 (s, 1H), 6.77 (s, 2H), 4.38 (s, 2H), 3.9-3.7 (m, 3H), 3.45 (s, 2H), 3.1-2.7 (m, 8H), 2.15 (s, 6H).</p> <p>- Mass : [LC/MS APCI+]: 383 (<math>\text{MH}^+</math>).</p>
262	-	racemic	<p>- <math>^1\text{H-NMR}</math> (CDCl<sub>3</sub>): 7.3-7.1 (m, 7H), 6.9-6.7 (m, 2H), 4.5 (s, 2H), 3.8-3.6 (m, 3H), 3.78 (s, 3H), 3.36 (s, 2H), 3.25-3.0 (m, 4H), 2.9-2.6 (m, 4H).</p> <p>- Mass : [LC/MS APCI+]: 385 (<math>\text{MH}^+</math>).</p>
263	-	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.45-7.25 (m, 5H), 7.16 (t, 1H), 6.73 (d, 2H), 6.67 (s, 1H), 4.44 (m, 1H), 4.41 (s, 2H), 3.85-3.65 (m, 3H), 3.35 (s, 2H), 3.1 (m, 4H), 2.7-2.5 (m, 4H), 1.18 (d, 6H).</p> <p>- Mass : [LC/MS APCI+]: 413 (<math>\text{MH}^+</math>).</p>
264	1 maleate . 1/3 H <sub>2</sub> O	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.4-7.2 (m, 9H), 6.14 (s, 4H), 4.52 (s, 2H), 4.2 (m, 1H), 4.05 (m, 1H), 3.9 (m, 1H), 3.68 (s, 2H), 3.2-3.0 (m, 4H), 3.0-2.8 (m, 4H).</p> <p>- Mass : [LC/MS APCI+]: 389 / 391 (<math>\text{MH}^+</math>).</p>
266	-	S	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.45 (t, 1H), 7.4-7.2 (m, 5H), 7.22 (d, 2H), 4.47 (s, 2H), 3.85 (dd, 1H), 3.73 (t, 1H), 3.66 (dd, 2H), 3.16 (s, 2H), 2.7 (m, 4H), 2.6-2.4 (m, 4H).</p> <p>- Mass : [LC/MS APCI+]: 423 / 425 / 427 (<math>\text{MH}^+</math>).</p> <p>- <math>[\alpha]_D = +8.9</math> (1% CH<sub>3</sub>OH, 25°C).</p>
267	-	R	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.45 (t, 1H), 7.4-7.2 (m, 5H), 7.22 (d, 2H), 4.47 (s, 2H), 3.85 (dd, 1H), 3.73 (t, 1H), 3.66 (dd, 2H), 3.14 (s, 2H), 2.65 (m, 4H), 2.6-2.4 (m, 4H).</p> <p>- Mass : [LC/MS APCI+]: 423 / 425 / 427 (<math>\text{MH}^+</math>).</p> <p>- <math>[\alpha]_D = +13.45</math> (1% CH<sub>3</sub>OH, 25°C).</p>
268	2 HCl	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.51 (d, 1H), 7.4 (m, 6H), 7.22 (d, 2H), 4.5 (s, 2H), 4.33 (t, 1H), 4.05-3.8 (m, 2H), 3.69 (s, 2H), 3.2-3.1 (m, 6H), 3.05 (m, 2H).</p> <p>- Mass : [LC/MS APCI+]: 423 / 425 / 427 (<math>\text{MH}^+</math>).</p>
269	2 maleate	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.74 (s, 1H), 7.45 (s, 2H), 7.40 (m, 5H), 6.15 (s, 4H), 4.52 (s, 2H), 4.05 (m, 1H), 3.9-3.8 (m, 2H), 3.78 (s, 2H), 3.1 (m, 4H), 2.8 (m, 4H).</p> <p>- Mass : [LC/MS APCI+]: 511 / 513 / 515 (<math>\text{MH}^+</math>).</p>
270	2 maleate	racemic	<p>- <math>^1\text{H-NMR}</math> (DMSO): 7.45 (d, 1H), 7.36 (s, 5H), 7.10 (m, 2H), 6.95 (d, 1H), 6.07 (s, 4H), 4.52 (s, 2H), 4.49 (s, 2H), 3.9 (m, 2H), 3.85 (m, 1H), 3.7-3.5 (m, 4H), 3.0-2.7 (m, 4H).</p> <p>- Mass : [LC/MS APCI+]: 391 (<math>\text{MH}^+</math>).</p>

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**Table VIIa – Physico-chemical properties of compounds of formula I**

Cpd No.	Free base/Salt	Stereochemistry	Analysis
271	1 maleate · 1 H <sub>2</sub> O	racemic	<p>- <sup>1</sup>H-NMR (DMSO): 7.84 (s, 1H), 7.61 (s, 1H), 7.44 (s, 1H), 7.4 (m, 5H), 6.22 (s, 4H), 4.48 (s, 2H), 4.1-3.7 (m, 5H), 3.2-3.0 (m, 6H), 2.9 (m, 2H).</p> <p>- Mass : [LC/MS APCI+]: 559/561 (MH<sup>+</sup>).</p>
272	2/3 H <sub>2</sub> O	racemic	<p>- <sup>1</sup>H-NMR (DMSO): 8.00 (s, 2H), 7.98 (s, 1H), 7.25 (m, 3H), 7.15 (m, 2H), 4.0-3.65 (m, 3H), 3.07 (s, 2H), 2.6-2.3 (m, 8H).</p> <p>- Mass : [LC/MS APCI+]: 491 (MH<sup>+</sup>).</p>
273	2 HCl · 3 H <sub>2</sub> O	NSA	<p>- <sup>1</sup>H-NMR (DMSO): 7.87 (s, 1H), 7.81 (s, 2H), 7.5-7.3 (m, 5H), 4.7 (q, 1H), 4.35 (t, 1H), 3.95 (dd, 1H), 3.77 (s, 2H), 3.57 (dd, 1H), 3.4-3.1 (m, 6H), 3.1-3.0 (m, 2H), 1.41 (d, 3H).</p> <p>- Mass : [LC/MS APCI+]: 505 (MH<sup>+</sup>).</p>
274	2 HCl · 1 H <sub>2</sub> O	NSB	<p>- <sup>1</sup>H-NMR (DMSO): 7.89 (s, 1H), 7.8 (s, 2H), 7.4-7.3 (m, 5H), 4.71 (q, 1H), 4.35 (t, 1H), 4.1-3.9 (dd, 1H), 3.8 (s, 2H), 3.65 (dd, 1H), 3.4-3.1 (m, 6H), 3.1-2.95 (m, 2H), 1.35 (d, 3H).</p> <p>- Mass : [LC/MS APCI+]: 505 (MH<sup>+</sup>).</p>
275	2 HCl · 5/2 H <sub>2</sub> O	S,R	<p>- <sup>1</sup>H-NMR (DMSO): 7.91 (s, 1H), 7.85 (s, 2H), 7.5-7.4 (m, 5H), 4.73 (q, 1H), 4.44 (t, 1H), 3.89 (s, 2H), 3.99 (m, 1H), 3.58 (m, 1H), 3.41 (m, 2H), 3.36 (m, 4H), 3.16 (m, 2H), 1.41 (d, 3H).</p> <p>- Mass : [LC/MS APCI+]: 505 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = +31,38; +23,65° (1% DMSO 25°C).</p>
276	2 HCl · 1 H <sub>2</sub> O	S,S	<p>- <sup>1</sup>H-NMR (DMSO): 7.93 (s, 1H), 7.82 (s, 2H), 7.4 (m, 5H), 4.70 (q, 1H), 4.35 (t, 1H), 4.00 (m, 1H), 3.78 (s, 2H), 3.66 (m, 1H), 3.23 (m, 4H), 3.20 (m, 2H), 3.04 (m, 2H), 1.35 (d, 3H).</p> <p>- Mass : [LC/MS APCI+]: 505 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = -14,33° (1% DMSO 25°C).</p>
277	2 HCl · 1 H <sub>2</sub> O	R,R	<p>- <sup>1</sup>H-NMR (DMSO): 7.92 (s, 1H), 7.82 (s, 2H), 7.4 (m, 5H), 4.71 (q, 1H), 4.34 (t, 1H), 4.00 (m, 1H), 3.79 (s, 2H), 3.66 (m, 1H), 3.23 (m, 4H), 3.20 (m, 2H), 3.04 (m, 2H), 1.36 (d, 3H).</p> <p>- Mass : [LC/MS APCI+]: 505 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = +13,41 (1% DMSO 25°C).</p>
278	2 HCl · 5/2 H <sub>2</sub> O	R,S	<p>- <sup>1</sup>H-NMR (DMSO): 7.91 (s, 1H), 7.84 (s, 2H), 7.5-7.4 (m, 5H), 4.72 (q, 1H), 4.44 (t, 1H), 3.89 (s, 2H), 3.99 (m, 1H), 3.58 (m, 1H), 3.41 (m, 2H), 3.36 (m, 4H), 3.16 (m, 2H), 1.40 (d, 3H).</p> <p>- Mass : [LC/MS APCI+]: 505 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = -31,66; -23,83° (1% DMSO 25°C).</p>

Table VIIa – Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereochemistry	Analysis
279	2 HCl . 1 H <sub>2</sub> O	S,R	<p>- <sup>1</sup>H-NMR (DMSO): 7.88 (s, 1H), 7.80 (s, 2H), 7.4-7.3 (m, 5H), 4.68 (q, 1H), 4.2-4.0 (m, 1H), 4.06 (s, 2H), 3.95-3.8 (m, 1H), 3.75 (t, 2H), 3.65-3.5 (m, 1H), 3.4-3.3 (m, 4H), 3.28 (t, 2H), 3.25-3.1 (m, 2H), 3.1-2.9 (m, 2H), 1.38 (d, 3H).</p> <p>- Mass : (LC/MS APCI+); 549 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = +26,55° (1% CH<sub>3</sub>OH, 25°C).</p>
280	2 HCl . 1 H <sub>2</sub> O	S,S	<p>- <sup>1</sup>H-NMR (DMSO): 7.89 (s, 1H), 7.79 (s, 2H), 7.5-7.3 (m, 5H), 4.69 (q, 1H), 4.26 (t, 1H), 4.1-3.95 (m, 1H), 4.05 (s, 2H), 3.75 (t, 2H), 3.7-3.6 (m, 4H), 3.5-3.3 (m, 4H), 3.29 (t, 2H), 3.3-3.15 (m, 2H), 3.15-3.0 (m, 2H), 1.34 (d, 3H).</p> <p>- Mass : (LC/MS APCI+); 549 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = -3,51 (1% CH<sub>3</sub>OH, 25°C).</p>
281	2 HCl . 1/2 H <sub>2</sub> O	R,R	<p>- <sup>1</sup>H-NMR (DMSO): 7.86 (s, 1H), 7.81 (s, 2H), 7.5-7.3 (m, 5H), 4.73 (q, 1H), 4.54 (t, 1H), 4.15-4.0 (m, 1H), 4.06 (s, 2H), 3.8-3.65 (m, 3H), 3.6-3.5 (m, 4H), 3.5-3.3 (m, 4H), 3.25-3.1 (m, 2H), 1.35 (d, 3H).</p> <p>- Mass : (LC/MS APCI+); 549 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = +1,77° (1% CH<sub>3</sub>OH, 25°C).</p>
282	2 HCl . 1/2 H <sub>2</sub> O	R,S	<p>- <sup>1</sup>H-NMR (DMSO): 7.89 (s, 1H), 7.80 (s, 2H), 7.4-7.3 (m, 5H), 4.68 (q, 1H), 4.1-4.0 (m, 1H), 4.06 (s, 2H), 3.95-3.8 (m, 1H), 3.74 (t, 2H), 3.6-3.5 (m, 1H), 3.4-3.3 (m, 4H), 3.26 (t, 2H), 3.15-3.0 (m, 2H), 3.0-2.85 (m, 2H), 1.37 (d, 3H).</p> <p>- Mass : (LC/MS APCI+); 549 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = -30,67° (1% CH<sub>3</sub>OH, 25°C).</p>
283	2 HCl . 3/2 H <sub>2</sub> O	racemic	<p>- <sup>1</sup>H-NMR (DMSO): 7.94 (s, 1H), 7.88 (s, 2H), 7.5-7.35 (m, 5H), 4.72 (s, 2H), 4.67 (m, 1H), 4.1-3.8 (m, 2H), 3.98 (s, 2H), 3.7-3.5 (m, 4H), 3.4-3.2 (m, 4H), 2.15-2.0 (m, 2H).</p> <p>- Mass : (LC/MS APCI+); 505 (MH<sup>+</sup>).</p>
284	2 maleate . 1 H <sub>2</sub> O	NSA	<p>- <sup>1</sup>H-NMR (DMSO): 8.11 (s, 1H), 8.0 (m, 2H), 7.89 (s, 2H), 7.7 (d, 1H), 7.55 (t, 1H), 7.4-7.25 (m, 5H), 6.14 (s, 4H), 4.7 (s, 2H), 4.31 (s, 2H), 4.16 (t, 1H), 4.0-3.8 (m, 2H), 3.2-2.95 (m, 6H), 3.85 (m, 2H), 1.9 (m, 2H).</p> <p>- Mass : (LC/MS APCI+); 581 (MH<sup>+</sup>).</p> <p>- [α]<sub>D</sub> = -5.80 (1% CH<sub>3</sub>OH, 25°C).</p>

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Table VIIa - Physico-chemical properties of compounds of formula I

Cpd No.	Free base/Salt	Stereo- chemistry	Analysis	
			1H-NMR (DMSO): 8.11 (s, 1H), 8.0 (m, 2H), 7.89 (s, 2H), 7.7 (d, 1H), 7.55 (t, 1H), 7.4-7.25 (m, 5H), 6.15 (s, 4H), 4.7 (s, 2H), 4.31 (s, 2H), 4.16 (t, 1H), 4.0-3.8 (m, 2H), 3.2-2.95 (m, 6H), 3.85 (m, 2H), 1.92 (m, 2H).	- Mass : [LC/MS APCI+]: 581 (MH <sup>+</sup> ). - [α] <sub>D</sub> = +2.30 (1% CH <sub>3</sub> OH, 25°C).
285	2 maleate . 1 H <sub>2</sub> O	NSB		
286	2 HCl . 2 H <sub>2</sub> O	racemic	1H-NMR (DMSO): 7.75 (s, 1H), 7.69 (s, 2H), 7.2 (m, 5H), 4.26 (t, 2H), 4.67 (m, 1H), 3.91 (dd, 2H), 3.84 (s 2H), 3.45-3.05 (m, 10H). - Mass : [LC/MS APCI+]: 507 (MH <sup>+</sup> ).	

1.4.3. Preparation of compounds of formula I according to process (a.3).

1.4.3.1. (2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetic acid isobutyl ester (compound 287) dichlorhydrate monohydrate.

**[0072]** In a round-bottomed flask fitted with a reflux condenser and a thermometer were introduced (2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetic acid (compound 235, 0.5 g, 0.84 mmoles) dissolved in THF (20 ml). To this solution cooled at 0°C were successively added isobutanol (0.155 ml, 1.68 mmoles), DMAP (0.01 g, 0.084 mmoles) and EDCI (0.177 g, 0.93 mmoles). The reaction mixture was stirred for 2 hours at 0°C and then allowed to reach room temperature and stirred overnight. The organic solution was washed with HCl 0.1N and water, dried over MgSO<sub>4</sub> and concentrated. The resulting oil was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>: 99.5/0.5/0.1 v/v/v) to yield (2-{4-[2-(3,5-Bis-trifluoromethylbenzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetic acid isobutyl ester (compound 287, 390 mg, 65%) which was converted into its dihydrochloride monohydrate salt by reaction with HCl in diethylether.

**[0073]** Analysis for dihydrochloride monohydrate salt of compound 287:

- <sup>1</sup>H-NMR (DMSO): 7.95 (s, 1H), 7.9 (s, 2H), 7.5-7.3 (m, 5H), 4.7 (dd, 2H), 4.4 (t, 1H), 4.1 (s, 2H), 4.05-3.85 (m, 2H), 3.8 (d, 2H), 3.85-3.7 (m, 2H), 3.55-3.05 (m, 10H), 1.7 (m, 1H), 0.8 (d, 6H).
- Mass : (LC/MS APCI+): 591 (MH<sup>+</sup>).

1.4.3.2. 4-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-butyramide (compound 288).

**[0074]** In a round-bottomed flask fitted with a reflux condenser are introduced 493 mg (0.9 mmoles) of 4-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-butyric acid ethyl ester (compound 138 prepared at example 1.4.1 above), 15 ml of formamide and 97 mg (1.8 mmoles) of sodium methoxide. The mixture is heated to 95°C for 4 hours, then 48 mg (0.9mmole) of sodium methoxide are added and the mixture is kept overnight at 85°C. The mixture is cooled and partitioned between diethyl ether (100 ml) and brine (100 ml). The organic phase is dried and volatile substances are removed under reduced pressure, affording 400 mg of 4-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-butyramide as a yellow oil (yield 86%). The dimaleate salt of compound 288 is prepared in 2-butanone (yield: 4.32 g as a white solid).

**[0075]** Analysis for dimaleate of compound 288:

- <sup>1</sup>H-NMR (DMSO): 8.00 (s, 1H), 7.87 (s, 2H), 7.44 (s, 1H), 7.33 (m, 5H), 6.95 (s, 1H), 4.68 (dd, 2H), 3.9.1-3.8 (m, 3H), 3.9-3.4 (m, 8H), 3.0 (t, 2H), 2.14 (t, 2H), 1.78 (m, 2H).
- Mass : (LC/MS APCI+): 518 (MH<sup>+</sup>).

1.4.3.3. (S)-{4-(2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl)-piperazin-1-yl}-acetonitrile dichlorhydrate (compound 291).

**[0076]** In a round-bottomed flask fitted with a reflux condenser and a thermometer were introduced 3 g (6.13 mmoles) of (S)-2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenylethyl]-piperazin-1-yl}-acetamide dissolved in 30 ml of CH<sub>2</sub>Cl<sub>2</sub> (compound 144 prepared at example 1.4.1 above). The solution was cooled to -78°C and DMSO (0.7 ml, 9.8 mmoles) and oxalyl chloride (0.6 ml, 7.4 mmoles) were added. After 15 minutes, triethylamine (2.5 ml, 18.4 mmoles) was added dropwise and the reaction mixture was stirred at -70°C until complete disappearance of the starting material. The reaction was quenched with water and the pH was adjusted to 11 by addition of aqueous NaOH. The aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The crude was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>: 98/2/0.2 v/v/v) to yield (S)-{4-[2-(3,5-Bis-trifluoromethylbenzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetonitrile (compound 291, 2.14 g, 73%) as a pale yellow powder which was converted into the dihydrochloride salt by reaction with HCl in diethylether.

**[0077]** Analysis for dihydrochloride of compound 291

- <sup>1</sup>H-NMR (DMSO): 7.95 (s, 1H), 7.9 (s, 2H), 7.55-7.35 (m, 5H), 4.72 (dd, 2H), 4.6 (t, 1H), 4.07 (d, 2H), 3.72 (s, 2H), 3.15 (m, 4H), 2.75 (m, 4H).
- Mass : (LC/MS APCI+): 472 (MH<sup>+</sup>).
- [α]D= +11.2° (1% CH<sub>3</sub>OH, 25°C).

1.4.3.4. 2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-N-methyl-acetamide (compound 292)

**[0078]** In a round-bottomed flask fitted with a reflux condenser and a thermometer are introduced 1.5 g (3 mmoles) of {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-acetic acid (compound 229 prepared at example 1.4.2 above), 7 ml of THF and 7 ml of acetonitrile. Then 1.85 ml (3.7 mmoles) of a 2M solution of methylamine in THF are added, followed by 234 mg (1.5 mmoles) of HOBT, 1.33 ml (7.6 mmoles) of diisopropylethylamine and 880 mg (4.3 mmoles) of DCC. The mixture is stirred until completion of the reaction, and filtered. Volatile substances are removed under reduced pressure, and the residue is partitioned between ethyl acetate and 0.1 N sodium hydroxide. The organic phase is washed with brine, dried over magnesium sulfate and volatile substances are removed under reduced pressure. This yields crude 2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-N-methyl-acetamide (compound 292) which is directly converted into its dimaleate salt in 2-butanone (1.44 g of a white solid; yield 65%).

**[0079]** The compounds 290, 293 and 294 (Table VIII) were obtained by the same method. Physico-chemical properties of the compounds of formula I prepared according to this method are given in Table VIIIA below. When the compounds of formula I are in the form of non toxic pharmaceutically acceptable salts, they are obtained by the general methods given above.

Table VIII -

Preparation of compounds 290, 293 and 294.				
Cpd No.	W	Stereo-chemistry	Conditions material I	Starting
290	H <sub>3</sub> COOC-CH <sub>2</sub> -NH-CO-CH <sub>2</sub> -	S	H <sub>2</sub> N-CH <sub>2</sub> -COOCH <sub>3</sub> , EDCI, HOBT	231
293	(tBu)NH-CO-CH <sub>2</sub> -	racemic	NH <sub>2</sub> tBu, EDCI, HOBT	229
294	(tBu)(CH <sub>3</sub> )NH-CO-CH <sub>2</sub> -	racemic	NtBuCH <sub>3</sub> , EDCI, HOBT	229

Table VIIIA -

Physico-chemical properties of compounds of formula I			
Cpd No.	Free base/Salt	Stereo chemistry	Analysis
292	2 maleate	racemic	<sup>1</sup> H-NMR (DMSO): 8.2 (s, 2H), 8.0 (s, 1H), 7.5 (m, 2H), 6.3 (s, 4H), 4.8 (s, 2H), 4.0-3.8 (m, 3H), 3.6 (m, 2H), 3.2-2.8 (m, 8H), 2.7 (s, 3H). SM (LC/MS APCI+): 504 (MH+).
293	2 maleate	racemic	<sup>1</sup> H-NMR (DMSO): 7.9 (s, 1H), 7.8 (s, 2H), 7.3 (m, 5H), 6.2 (s, 4H), 4.7 (s, 2H), 3.9 (m, 3H), 3.5 (m, 2H), 2.6-3.2 (m, 8H), 1.2 (s, 9H). SM (LC/MS APCI+): 546 (MH+).
294	2 maleate	racemic	<sup>1</sup> H-NMR (DMSO): 7.97 (s, 1H), 7.87 (s, 2H), 7.35 (m, 5H), 6.13 (s, 4H), 4.68 (s, 2H), 4.12 (s, 2H), 4.0-3.8 (m, 3H), 3.3-3.0 (m, 6H), 2.79 (s, 3H), 2.75 (m, 2H), 1.37 (s, 9H). SM (LC/MS APCI+): 560 (MH+).

## 1.4.4. Preparation of compounds of formula I according to process (a.4).

**[0080]** 5-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-ylmethyl]-2,4-dihydro-[1,2,4]triazol-3-one (compound 295) is prepared by reacting 1-(2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl)-piperazine (compound 86 prepared at example 1.3.1 above) with N'-(2-Chloro-1-imino-ethyl)-hydrazinecarboxylic acid methyl ester according to the procedure described by Ladduwahetty T. et al., J. Med. Chem. (1996), 39, 2907-2914.

**[0081]** Analysis for compound 295:

- <sup>1</sup>H-NMR (DMSO): 7.95 (s, 1H), 7.85 (s, 2H), 7.35-7.25 (m, 5H), 4.65 (s, 2H), 3.9 (dd, 1H), 3.8 (dd, 1H), 3.65 (t, 1H), 3.21 (s, 2H), 2.5-2.35 (m, 8H).
- Mass : (LC/MS APCI+): 530 (MH<sup>+</sup>).

## 1.4.5. Preparation of compounds of formula I according to process (a.5).

**[0082]** In a round-bottomed flask fitted with a reflux condenser and a thermometer 7.2 g (14 mmoles) of (S)-5-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-pentanenitrile (compound 153, prepared at example 1.4.1 above), 25 ml of toluene, 3.9 g (15 mmoles) of dibutyl tin oxide, and 3.3 g (28 mmoles) of trimethyl silyl azide were introduced. The mixture was heated at reflux for 18 hours, the volatile substances were removed under reduced pressure and the residue was washed with methyl alcohol, affording 11.4 g of crude product. The product was purified by chromatography on silica gel (eluant : methylene chloride-methanol-aqueous ammonia 90/10/1 (v/v/v)), affording 6.2 g of an oil (yield 80%). The product was dissolved in 50 ml of diisopropyl ether, the solution was filtered, and 13 ml of a 1.88N solution of hydrochloric acid in diethyl ether were added to the filtrate. The mixture was stirred for 16 hours and filtered. The precipitate was collected and recrystallized from acetonitrile, affording 4.2 g of (S)-1-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine (compound 298) as its dihydrochloride. Yield: 48%.

**[0083]** The compounds listed in Table IX were obtained by the same method. Physico-chemical properties of the compounds of formula I prepared according to this method are given in Table IXa below. When the compounds of formula I are in the form of non toxic pharmaceutically acceptable salts, they are obtained by the general methods given above.

Table IX -

Preparation of compounds of formula by process (a.2)								
Cpd No.	Stereo-chemistry	n"	R2	Ar <sup>1</sup>	Ar <sup>2</sup>	Z	W*	Starting
								cpd No
296	S 1		H	phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-CH <sub>2</sub> -	291
297	racemic	1	H	phenyl	3,5-bis (trifluoromethyl)-phenyl	G	Tet-(CH <sub>2</sub> ) <sub>4</sub> -	152
299	R	1	H	phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-(CH <sub>2</sub> ) <sub>4</sub> -	154
300	racemic	1	H	phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-CH <sub>2</sub> O (CH <sub>2</sub> ) <sub>2</sub> -	155

\*Tet means tetrazol.

Table IX - (continued)

Preparation of compounds of formula by process (a.2)								
Cpd No.	Stereo-chemistry	n"	R2	Ar <sup>1</sup>	Ar <sup>2</sup>	Z	W*	Starting
								cpd No
301	racemic	1	H	4-fluoro-phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-(CH <sub>2</sub> ) <sub>4</sub> -	185
302	NSA	1	CH <sub>3</sub>	phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-(CH <sub>2</sub> ) <sub>4</sub> -	212
303	NSB	1	CH <sub>3</sub>	phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-(CH <sub>2</sub> ) <sub>4</sub> -	213
304	racemic	1	CH <sub>3</sub>	phenyl	3,5-bis (trifluoromethyl)-phenyl	O	Tet-(CH <sub>2</sub> ) <sub>5</sub> -	156

\*Tet means tetrazol.

Table IXa -

Physico-chemical properties of compounds of formula I.				
Cpd No.	Stereo-chemistry	Salt	Characteristics	
296	S	2 HCl . 1 H <sub>2</sub> O	<sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.85 (s, 2H), 7.55-7.35 (m, 5H), 4.7 (s, 2H), 4.55 (t, 1H), 4.1-3.9 (m, 4H), 3.3 (m, 2H), 3.1 (m, 2H), 2.8 (m, 4H). SM (LC/MS APCI+): 515 (MH+). [α] <sub>D</sub> = +19 (1% CH <sub>3</sub> OH, 25°C).	
297	racemic	2 HCl	<sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.81 (s, 2H), 7.35 (m, 5H), 4.66 (s, 2H), 4.2 (m, 1H), 4.1-3.9 (m, 2H), 3.4-3.2 (m, 4H), 3.2-2.9 (m, 6H), 2.89 (t, 2H), 1.7-1.5 (m, 4H). SM (LC/MS APCI+): 557 (MH+)	
298	S	2 HCl	<sup>1</sup> H-NMR (DMSO): 7.95 (s, 1H), 7.9 (s, 2H), 7.55 (m, 2H), 7.4 (m, 3H), 4.7 (s, 2H), 4.6 (t, 1H), 4.1-3.9 (m, 2H), 3.55-2.85 (m, 12H), 1.8-1.55 (m, 4H). SM (LC/MS APCI+): 557 (MH+). [α] <sub>D</sub> = +16 (1% CH <sub>3</sub> OH, 25°C).	
299	R	2 HCl	<sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.83 (s, 2H), 7.45-7.35 (m, 5H), 4.68 (s, 2H), 4.68 (t, 1H), 4.05-3.9 (m, 2H), 3.4-3.25 (m, 4H), 3.15-2.85 (m, 8H), 1.8-1.55 (m, 4H). SM (LC/MS APCI+): 557 (MH+). [α] <sub>D</sub> = +18.95 (1% CH <sub>3</sub> OH, 25°C).	
300	racemic	2 HCl	<sup>1</sup> H-NMR (DMSO): 7.92 (s, 1H), 7.83 (s, 2H), 7.45-7.35 (m, 5H), 4.85 (s, 2H), 4.67 (s, 2H), 4.25 (t, 1H), 4.1-	

Table IXa - (continued)

Physico-chemical properties of compounds of formula I.			
Cpd No.	Stereo-chemistry	Salt	Characteristics
5			3.75 (m, 4H), 3.45-3.25 (m, 6H), 3.2-2.9 (m, 4H). SM (LC/MS APCI+): 559 (MH+).
10	301	racemic 2 HCl. 1/3 C <sub>3</sub> H <sub>8</sub> O	<sup>1</sup> H-NMR (DMSO): 7.98 (s, 1H), 7.9 (s, 2H), 7.6 (m, 2H), 7.25 (t, 2H), 4.72 (s, 2H), 4.45 (m, 1H), 4.15 (m, 1H), 3.95 (m, 1H), 3.75 (se, 1/3H), 3.6-3.0 (m, 10H), 2.92 (t, 2H), 1.8-1.6 (m, 4H), 1.04 (d, 2H). SM (LC/MS APCI+): 575 (MH+).
15	302	NSA 2 HCl	<sup>1</sup> H-NMR (DMSO): 7.9 (s, 1H), 7.8 (s, 2H), 7.45-7.25 (m, 5H), 4.7 (q, 1H), 4.3 (t, 1H), 4.05 (dd, 1H), 3.65 (dd, 1H), 3.5-2.95 (m, 10H), 2.9 (t, 2H), 1.7-1.55 (m, 4H), 1.35 (d, 3H). SM (LC/MS APCI+): 571 (MH+).
20	303	NSB 2 HCl	<sup>1</sup> H-NMR (DMSO): 7.91 (s, 1H), 7.81 (s, 2H), 7.45-7.25 (m, 5H), 4.7 (q, 1H), 4.28 (t, 1H), 4.05 (dd, 1H), 3.65 (dd, 1H), 3.5-2.95 (m, 10H), 2.9 (t, 2H), 1.7-1.55 (m, 4H), 1.35 (d, 3H). SM (LC/MS APCI+): 571 (MH+).
25	304	racemic 2 maleate	<sup>1</sup> H-NMR (DMSO): 7.97 (s, 1H), 7.87 (s, 2H), 7.35 (m, 5H), 6.14 (s, 4H), 4.69 (s, 2H), 4.05-3.8 (m, 3H), 3.3-3.1 (m, 4H), 3.04 (t, 2H), 2.91 (t, 2H), 2.8-2.6 (m, 4H), 2.04 (t, 2H), 1.85-1.7 (m, 2H), 1.7-1.5 (m, 2H), 1.32 (m, 2H). SM (LC/MS APCI+): 571 (MH+).
30			
35			

## 1.4.6. Preparation of compounds of formula I according to process (a.6).

## 1.4.6.1. Synthesis of N-[{2-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenylethyl]-piperazin-1-yl}-ethoxy]-acetyl]-methanesulfonamide (compound 305).

**[0084]** In a round-bottomed flask fitted with a reflux condenser and a thermometer, 0.5 g (0.8 mmoles) of the dihydrochloride of (2-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-ethoxy)-acetic acid (compound 235) and 10 ml of dichloromethane, were introduced under nitrogen. The solution was cooled to 0°C and 0.1 ml (1.2 mmoles) of oxalyl chloride were added. The reaction mixture was stirred at room temperature for one night. Again, 1ml (12 mmoles) of oxalyl chloride were added. After 2 hours, the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane and a solution of 0.075 g (0.8 mmoles) of methanesulfonamide and 0.12ml (0.8 mmoles) of triethylamine in 5 ml of tetrahydrofuran, were added dropwise. The mixture was stirred at room temperature for one night. The solution was washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure affording 0.33 g of crude product. This was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub> / CH<sub>3</sub>OH: 95/5) affording 0.129 g of an oil. This oil was dissolved in methanol and was filtered on dicalite ; 0.4ml of HCl 1N and water were added. The mixture was concentrated under reduced pressure, lyophilized and dried under high vacuum at 50°C, affording 0.087 g (14%) of a white powder as the hydrated (3/2 H<sub>2</sub>O) dihydrochloride of N-[{2-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy]-acetyl]-methanesulfonamide (compound 305).

**[0085]** Analysis for hydrated (3/2 H<sub>2</sub>O) dihydrochloride of compound 305:

- <sup>1</sup>H-NMR (DMSO): 7.92 (s, 1H), 7.81 (s, 2H), 7.35 (m, 5H), 4.66 (s, 2H), 4.08 (m, 3H), 4.0-3.9 (m, 2H), 3.75 (t, 2H),

3.4-3.2 (m, 6H), 3.2 (s, 3H), 3.1-2.8 (m, 4H).

- Mass (LC/MS APCI+): 612 (MH+).

5 1.4.6.2. N-[(2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetyl]-benzenesulfonamide (compound 306).

[0086] In a round-bottomed flask fitted with a reflux condenser and a thermometer was introduced (2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetic acid (compound 235 prepared at example 1.4.2; 2.7 g, 4.54 mmoles) dissolved in  $\text{CH}_2\text{Cl}_2$  (25 ml). Benzenesulphonamide (1.07 g, 6.8 mmoles), DMAP (10 mg, 0.45 mmoles) and EDCI (0.96 g, 5 mmoles) were added to the solution and the reaction mixture was stirred at room temperature for 48 hours. The organic solution was washed with HCl 0.1N and brine, dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by chromatography on silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ : 95/5/0.2 v/v/v) to afford the monohydrate of N-[(2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethoxy)-acetyl]-benzenesulfonamide (compound 306; 1.5 g, 50%) as a beige solid.

15 [0087] Analysis for the monohydrate of compound 306:

- $^1\text{H-NMR}$  (DMSO): 7.85 (s, 1H), 7.72 (s, 2H), 7.68 (dd, 2H), 7.4-7.25 (m, 8H), 4.64 (s, 2H), 4.05-3.75 (m, 2H), 3.76 (s, 2H), 3.7-3.6 (m, 3H), 3.2-3.0 (m, 6H), 2.8-2.55 (m, 4H).
- Mass: (LC/MS APCI+): 674 (MH+).

20 1.4.7. Preparation of compounds of formula I according to process (a.7).

[0088] N-p-toluenesulfonic-carbamic acid 2-{4-[2-(3,5-bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethyl ester (compound 307).

25 [0089] In a round-bottomed flask fitted with a reflux condenser and a thermometer was introduced compound 2-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethanol (compound 157 prepared at example 1.4.1; 0.5 g, 0.99 mmoles) dissolved in  $\text{CH}_2\text{Cl}_2$  (5 ml). p-toluenesulfonylisocyanate (0.14 ml, 1.09 mmoles) was added to the solution and the reaction mixture was stirred at room temperature. The organic solution was washed with  $\text{NaHCO}_3$  and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by chromatography on silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ : 95/5/0.2) to give N-p-toluenesulfonic-carbamic acid 2-{4-[2-(3,5-bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-ethyl ester (compound 307; 400 mg, 60%) which was converted into its dihydrochloride salt by reaction with HCl in diethylether (Friesen R.W. and Phipps L.G., Synlett (1991), 420-422).

30 [0090] Analysis for the dihydrochloride of compound 307:

- $^1\text{H-NMR}$  (DMSO): 7.91 (s, 1H), 7.82 (s, 2H), 7.74 (d, 2H), 7.4 (m, 5H), 7.38 (d, 2H), 4.67 (s, 2H), 4.24 (m, 3H), 4-3.9 (m, 1H), 3.3-3.05 (m, 8H), 3.05-2.9 (m, 2H), 2.33 (s, 3H).
- Mass : (LC/MS APCI+): 674 (MH+).

40 1.4.8. Preparation of compounds of formula I according to process (a.8).

[0091] N-(3-{4-[2-(3, 5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-1-phenyl-propyl)-acetamide (compound 308).

45 [0092] In a round-bottomed flask fitted with a reflux condenser and a thermometer, 1.55 g (2.73 mmoles) of 3-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-1-phenyl-propan-1-ol (compound 169 prepared at example 1.4.1 above) and 3.6 ml of acetonitrile were introduced. The mixture was cooled to 0°C and 3 ml of  $\text{H}_2\text{SO}_4$  12N were added dropwise. The reaction was stirred at room temperature for 4 hours. Cold water was added and a solution of NaOH 6N was added until pH 7. The mixture was filtered, and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over magnesium sulfate, and concentrated under reduced pressure, affording 1.41g of crude product. Purification by chromatography on silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ , 97/3/03, (v/v/v)) gave 1.1 g of an oil which was dissolved in 10 ml of diisopropylether ; 1.75 ml of a solution 1.88N of HCl in ether was added affording, after filtration, 0.82g of the hydrated (5/4  $\text{H}_2\text{O}$ ) dihydrochloride of N-(3-{4-[2-(3, 5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl}-1-phenyl-propyl)-acetamide (compound 308) as a white powder.

50 [0093] Analysis for the hydrated (5/4  $\text{H}_2\text{O}$ ) dihydrochloride of compound 308

- $^1\text{H-NMR}$  (DMSO): 8.43 (d, 1H), 7.93 (s, 1H), 7.5-7.3 (m, 5H), 7.3-7.15 (m, 5H), 4.83 (t, 1H), 4.7 (s, 2H), 4.4 (t, 1H), 4.1 (dd, 1H), 3.95 (dd, 1H), 3.5-3.0 (m, 10H), 2.05 (m, 2H), 1.86 (s, 3H).
- Mass : (LC/MS APCI+): 608 (MH+).

## 1.4.9. Preparation of compounds of formula I according to process (a.9).

**[0094]** a. Following the procedure described in Maryanoff B.E. et al., J. Med Chem. (1981), 24 (1), 79-88: cis- and trans-4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-cyclohexanecarboxylic acid ethyl ester (compounds 310 and 311).

**[0095]** In a round-bottomed flask fitted with a reflux condenser and a thermometer was introduced 1-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazine (compound 86 prepared at example 1.3.1 above; 2.5 g, 5.8 mmol) dissolved in MeOH (30 ml). Acetic acid (0.43 ml, 7.52 mmoles), ethyl-4-oxocyclohexanecarboxylate (3.7 ml, 23 mmoles) and NaBH<sub>3</sub>CN (0.55 g, 8.7 mmoles) were added to the solution and the reaction mixture was heated at 50°C. MeOH was evaporated in vacuo and the residue was taken up in water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The crude was purified by chromatography on silica gel (eluent:Hex/AcOEt: 30/70 v/v) to give cis- and trans-4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-cyclohexanecarboxylic acid ethyl ester (compound 309; 3 g, 88%), which was separated by chiral HPLC (Chiralpak AD, eluent: MeOH/EtOH/Benzine/DEA: 8/2/90/0.1 v/v/v/v) into its cis and trans isomers (compounds 310 and 311). It was impossible by NMR to determine which of these two compounds has the cis-conformation and which has the trans-configuration.

**[0096]** b. Cis- and trans-4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-cyclohexanecarboxylic acid dichlorhydrate (compounds 312 and 313).

**[0097]** In a round-bottomed flask fitted with a reflux condenser and a thermometer were introduced cis- or trans-4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-cyclohexanecarboxylic acid ethyl ester (compound 310 prepared at example 1.4.9; 0.9 g, 1.53 mmoles), HCl 1N (8 ml) and the solution was added at reflux overnight. The pH of the solution was adjusted to 5-6 by addition of aqueous NaOH and was extracted with AcOEt. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The crude was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>: 90/10/0.5 then 85/15/1 v/v/v) to afford cis- or trans-4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-cyclohexanecarboxylic acid (compounds 312 or 313) as a pale yellow solid (0.4 g, 50%) which was converted into the dihydrochloride salt by reaction with HCl in diethylether. It was impossible by NMR to determine which of these two compounds has the cis-conformation and which has the trans-configuration.

**[0098]** Analysis for the dihydrochloride of compound 312:

- <sup>1</sup>H-NMR (DMSO): 8.01 (s, 1H), 7.93 (s, 2H), 7.53 (m, 2H), 7.43 (m, 3H), 4.73 (dd, 2H), 4.64 (t, 1H), 4.16 (dd, 1H), 3.99 (dd, 1H), 3.77 (m, 2H), 3.56 (m, 2H), 3.46 (m, 2H), 3.24 (m, 1H), 3.13 (m, 2H), 2.18 (m, 1H), 2.01 (m, 1H), 1.99 (m, 1H), 1.44 (m, 1H), 1.33 (m, 1H).
- Mass : (LC/MS APCI+): 559 (MH<sup>+</sup>).

**[0099]** Analysis for the dihydrochloride of compound 313:

- <sup>1</sup>H-NMR (DMSO): 8.0 (s, 1H), 7.88 (s, 2H), 7.42 (m, 5H), 4.70 (dd, 2H), 4.33 (t, 1H), 4.00 (dd, 1H), 3.92 (dd, 1H), 3.54 (m, 2H), 3.21 (m, 2H), 3.17 (m, 1H), 2.84 (m, 2H), 2.74 (m, 2H), 2.58 (m, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.51 (m, 1H), 1.37 (m, 1H).
- Mass : (LC/MS APCI+): 559 (MH<sup>+</sup>).

## 1.4.10. Preparation of compounds of formula I according to process (a.10).

**[0100]** 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-hexanoic acid (2,4-dimethoxybenzyloxy)-amide (compound 314).

**[0101]** In a round-bottomed flask, 0.85 g (1.55 mmoles) of 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-hexanoic acid (compound 234), 0.28g (2.02 mmoles) of hydroxybenzotriazole, 0.427 g (2.33 mmoles) of 2,4-dimethoxy-benzylhydroxylamine (obtained as described in B. Barlaam, A. Hamon, M. Maudet, Tetrahedron Lett (1998), 39, 7865-7868) and 0.456 g (2.33 mmoles) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, were introduced. The mixture was stirred at room temperature for 21 hours. The mixture was diluted with 40 ml of EtOAc and washed with water, saturated sodium bicarbonate, brine, dried over magnesium sulfate and concentrated under reduced pressure affording 1.27 g of crude product. Purification by chromatography on silica gel (eluent: ethylacetate/CH<sub>3</sub>OH 94/6) gave 71% of 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenylethyl]-piperazin-1-yl]-hexanoic acid (2,4-dimethoxy-benzyloxy)-amide (compound 314).

**[0102]** Analysis for compound 314:

- <sup>1</sup>H-NMR (DMSO): 7.94 (s, 1H), 7.84 (s, 2H), 7.2 (m, 6H), 6.5 (m, 2H), 4.68 (s, 2H), 4.64 (s, 2H), 3.89 (m, 1H), 3.75 (m, 7H), 3.6 (m, 1H), 2.45-2.2 (m, 9H), 2.12 (t, 2H), 1.88 (t, 2H), 1.45 (m, 2H), 1.33 (m, 2H), 1.23 (m, 2H).

- Mass : (LC/MS APCI+): 712 (MH+)

**[0103]** - 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-hexanoic acid hydroxyamide (compound 315) is prepared by deprotection of the O-protected hydroxamate 314 by trifluoroacetic acid:

**[0104]** In a round-bottomed flask fitted with a reflux condenser and a thermometer, 0.97 g (1.36 mmoles) of 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-hexanoic acid (2,4-dimethoxy-benzyloxy)-amide (compound 314) in 10 ml 5% TFA-dichloromethane solution, was stirred at room temperature during one day. Again, 1ml of TFA was added. The reaction mixture turned deep purple. The mixture was evaporated in vacuum, diluted in CH<sub>3</sub>OH and filtered to remove insoluble material. Evaporation of the filtrate gave 1.17 g of a brown oil which was purified by chromatography on silica gel affording 0.21 g of 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl]-hexanoic acid hydroxyamide (compound 315) transformed to its dimaleate salt by adding 0.085 g of maleic acid.

**[0105]** Analysis for monohydrated dimaleate of compound 315 :

- <sup>1</sup>H-NMR (DMSO): 7.96 (s, 1H), 7.86 (s, 2H), 7.3 (m, 5H), 6.11 (s, 4H), 4.67 (s, 2H), 3.9-3.8 (m, 3H), 3.5-2.6 (m, 10H), 1.94 (s, 2H), 1.6-1.4 (m, 4H), 1.25 (m, 2H).  
- Mass: (LC/MS APCI+): 562 (MH+)

Example 2. Preparation of compounds of formula I according to process (b).

**[0106]** 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-methoxycarbonylmethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester (compound 316).

**[0107]** Following the method described in Lin C.-H. et al., J. Med. Chem. (1993), 36, 2208-2218:

**[0108]** In a round-bottomed flask fitted with a reflux condenser and a thermometer were introduced {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-bromo-phenyl)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 184 prepared at example 1.4.1 above; 0.5 g, 0.8 mmoles), Et<sub>3</sub>N (0.26 ml, 1.8 mmoles), MeOH (3 ml) and DMF (9 ml). The mixture was purged with N<sub>2</sub> and a stream of CO was passed into the mixture for 10 min. A solution of Pd(OAc)<sub>2</sub> (19.2 mg, 10% moles) and Diphenylphosphinopropane (Dppp) (33 mg, 10% moles) dissolved in MeOH/DMF 1/3 (0.65 ml), purged with N<sub>2</sub>, was then added to the mixture. The reaction mixture was heated at 70°C and CO was bubbled through the reaction mixture overnight. The reaction mixture was purged with N<sub>2</sub>, quenched with NaHCO<sub>3</sub> and extracted with AcOEt. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give an oil which was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>: 99.5/0.5/0.1 v/v/v) to afford 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-methoxycarbonylmethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester (compound 316; 150 mg, 30%).

**[0109]** Analysis for compound 316:

- <sup>1</sup>H-NMR (DMSO): 7.95 (s, 2H), 7.90 (s, 1H), 7.75 (d, 2H), 7.45 (d, 2H), 4.65 (s, 2H), 4.0-3.65 (m, 3H), 3.90 (s, 3H), 3.60 (s, 3H), 3.15 (s, 2H), 2.60-2.30 (m, 8H).

Example 3. Preparation of compounds of formula I according to process (c).

**[0110]** (4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-cyano-phenyl)-ethyl]-piperazin-1-yl)-acetic acid methyl ester (compound 317).

**[0111]** Following the method described in Tschaen D.M. et al., JOC (1995), 60, 4324-4330:

**[0112]** A round-bottomed flask charged with Pd(OAc)<sub>2</sub> (36 mg, 4% moles) and P(o-tol)<sub>3</sub> (192 mg, 20% mol) was evacuated and then vented to nitrogen. N-methylpyrrolidone (NMP) (4 ml) was added and the mixture was heated at 50°C for 30 min. Diethylzinc in hexane (0.29 ml) was added and the mixture was maintained at 50°C for an additional 30 min. The mixture was cannulated into a flask containing a solution of {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-bromo-phenyl)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 184 prepared at example 1.4.1 above; 2.33 g, 4.0 mmoles) and Zn(CN)<sub>2</sub> (0.47 g, 4.0 mmoles) dissolved in NMP (6 ml). The reaction mixture was heated at 60°C for 3 hours. The eluent was evaporated and the residue was taken up in diethylether. The precipitate was filtered and the organic solution was washed with ammonium hydroxyde, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by chromatography on silica gel (eluent: Hex/AcOEt: 75/25 v/v) to give {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-cyano-phenyl)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 317; 0.9 g, 34%).

**[0113]** Analysis for compound 317:

- <sup>1</sup>H-NMR (DMSO): 7.95 (s, 1H), 7.85-7.75 (m, 4H), 7.50 (d, 2H), 4.65 (s, 2H), 3.95-3.65 (m, 3H), 3.60 (s, 3H), 3.15 (s, 2H), 2.60-2.30 (m, 8H).  
- Mass : (LC/MS APCI+): 530(MH+)

Example 4. Preparation of compounds of formula I according to process (d).

[0114] 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carboxymethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester hemihydrate (compound 318).

[0115] In a round-bottomed flask was introduced 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-methoxycarbonylmethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester (compound 316 prepared at example 2 above; 2.17 g, 3.86 mmoles) dissolved in MeOH (30 ml). To this solution cooled at 0°C was added KOH (0.54 g, 9.62 mmoles) dissolved in MeOH (20 ml). The reaction mixture was allowed to stand at room temperature overnight. The reaction was cooled to 0°C, quenched by addition of HCl 0.1 N and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/H<sub>2</sub>O: 95/5/0.5) to yield 4-[2-(3,5-bis-trifluoromethyl-benzyloxy)-1-(4-carboxymethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester hemihydrate (compound 318; 1.5 g, 71%).

[0116] Analysis for the hemihydrate of compound 318:

- <sup>1</sup>H-NMR (DMSO): 7.93 (s, 1H), 7.90 (d, 2H), 7.79 (s, 2H), 7.47 (d, 2H), 4.65 (s, 2H), 3.95-3.7 (m, 2H), 3.85 (s, 3H), 3.72 (t, 1H), 3.08 (s, 2H), 2.65-2.45 (m, 8H).
- Mass : (LC/MS APCI+): 549 (MH<sup>+</sup>).

[0117] 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carboxymethyl-piperazin-1-yl)-ethyl]-benzoic acid hemihydrate (compound 319).

[0118] In a round-bottomed flask were introduced 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-methoxycarbonylmethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester (compound 316 prepared at example 2; 2 g, 3.56 mmoles), KOH (0.4 g, 7.12 mmoles) and MeOH. The reaction mixture was heated at 60°C for 6 hours. MeOH was removed under reduced pressure and the residue was taken up by water. The pH was adjusted to 3-4 and the solution was extracted with AcOEt. The organic combined layers were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/H<sub>2</sub>O: 90/10/1 v/v/v) to give 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carboxymethyl-piperazin-1-yl)-ethyl]-benzoic acid hemihydrate (compound 319; 0.88 g, 45%).

[0119] Analysis for the hemihydrate of compound 319:

- <sup>1</sup>H-NMR (DMSO): 7.93 (s, 1H), 7.90 (d, 2H), 7.81 (s, 2H), 7.43 (d, 2H), 4.65 (s, 2H), 3.85 (dd, 1H), 3.8 (dd, 1H), 3.72 (t, 1H), 3.09 (s, 2H), 2.65-2.45 (m, 8H).
- Mass : (LC/MS APCI+): 535 (MH<sup>+</sup>).

[0120] {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carbamoyl-phenyl)-ethyl]-piperazin-1-yl}-acetic acid (compound 321) and {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carbamoylmethyl-piperazin-1-yl)-ethyl]-benzamide (compound 322).

[0121] In a small autoclave, 1.5 g (2.73 mmoles) of 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carboxymethyl-piperazin-1-yl)-ethyl]-benzoic acid methyl ester (compound 318) were dissolved in methanol. The solution was saturated with NH<sub>3</sub> and heated at 100°C for three days. Methanol was then evaporated and the crude product was purified by chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>: 80/20/0.5 v/v/v) to give 880 mg of {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carbamoyl-phenyl)-ethyl]-piperazin-1-yl}-acetic acid (compound 321) as a grey solid. 4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-carbamoylmethyl-piperazin-1-yl)-ethyl]-benzamide (compound 322) was isolated as a side product (150 mg).

[0122] Analysis for compound 321:

- <sup>1</sup>H-NMR (DMSO): 7.95 (s, 1H), 7.85-7.8 (m, 5H), 7.38 (d, 2H), 7.2 (s, 1H), 4.66 (s, 2H), 3.95-3.6 (m, 3H), 3.02 (s, 2H), 2.65-2.35 (m, 8H).
- Mass : (LC/MS APCI+): 534 (MH<sup>+</sup>).

[0123] Analysis for compound 322:

- <sup>1</sup>H-NMR (DMSO): 7.96 (s, 1H), 7.85 (s+d, 3H), 7.37 (d, 2H), 7.2 (s, 1H), 7.0-6.9 (s+s, 2H), 4.67 (s, 2H), 3.92 (dd, 1H), 3.82 (dd, 1H), 3.71 (t, 1H), 2.79 (s, 2H), 2.55-2.35 (m, 8H).
- Mass : (LC/MS APCI+): 533 (MH<sup>+</sup>).

Example 5. Preparation of compounds of formula I according to process (f).

[0124] Dihydrochloride of {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-cyano-phenyl)-ethyl]-piperazin-1-yl}-acetic

acid (compound 320).

[0125] In a round-bottomed flask were introduced compound {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-cyano-phenyl)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 317 prepared at example 2; 0.9 g, 1.7 mmoles), KOH (0.24 g, 4.25 mmoles) and MeOH. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and the pH was adjusted to 3. The solution was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was crystallized from diethylether/HCl to give the dihydrochloride of {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(4-cyano-phenyl)-ethyl]-piperazin-1-yl}-acetic acid (compound 320; 0.8 g, 80%).

[0126] Analysis for the dihydrochloride of compound 320:

- $^1\text{H-NMR}$  (DMSO): 7.86 (s, 1H), 7.71 (d, 2H), 7.62 (s, 2H), 7.52 (d, 2H), 4.58 (s, 2H), 4.1-3.8 (m, 3H), 3.72 (s, 2H), 3.35-3.15 (m, 4H), 2.9-2.4 (m, 4H).
- Mass : (LC/MS APCI+): 516 (MH+).

Example 6. Preparation of compounds of formula I according to process (g).

{4-[1-(2-Amino-phenyl)-2-(3,5-bis-trifluoromethyl-benzyloxy)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 323)

[0127] In a round-bottomed flask fitted with a reflux condenser and a thermometer were introduced {4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-(2-nitro-phenyl)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 190 prepared at example 1.4.1 above; 2 g, 3.64 mmoles),  $\text{SnCl}_2$  (3.45 g, 18.2 mmoles) and MeOH (40 ml) and the reaction mixture was heated at 60°C for 3 hours. MeOH was evaporated in vacuo and the crude was taken up in water. The pH was adjusted to 8-9 by addition of aqueous NaOH and the solution was extracted with AcOEt. The combined organic phases were dried over  $\text{MgSO}_4$  and concentrated. The resulting oil was purified by chromatography on silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ : 99/1/0.1 v/v/v) to yield {4-[1-(2-Amino-phenyl)-2-(3,5-bis-trifluoromethyl-benzyloxy)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 323; 1.7 g, 90%) as a yellow oil.

[0128] Analysis for compound 323:

- $^1\text{H-NMR}$  (DMSO): 7.95 (s, 1H), 7.90 (s, 2H), 6.95 (t, 1H), 6.55-6.45 (m, 3H), 4.90 (s, NH<sub>2</sub>), 4.65 (s, 2H), 3.85 (dd, 1H), 3.65 (dd, 1H), 3.40 (t, 1H), 3.15 (s, 2H), 2.55-2.35 (m, 8H).
- Mass : (LC/MS APCI+): 520 (MH+).

{4-[1-(2-Amino-phenyl)-2-(3,5-bis-trifluoromethyl-benzyloxy)-ethyl]-piperazin-1-yl}-acetic acid (compound 324)

[0129] In a round-bottomed flask were introduced {4-[1-(2-Amino-phenyl)-2-(3,5-bis-trifluoromethyl-benzyloxy)-ethyl]-piperazin-1-yl}-acetic acid methyl ester (compound 323; 1.3 g, 2.5 mmoles), KOH (0.35 g, 6.3 mmoles) and MeOH (20 ml). The reaction mixture was stirred at room temperature for 6 hours. MeOH was removed under reduce pressure and the residue was taken up in water. The pH was adjusted to 6 and the solution was extracted with  $\text{CH}_2\text{Cl}_2$ .

The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated. The residue (1.1 g, 88%) was recrystallized from diethylether to give {4-[1-(2-Amino-phenyl)-2-(3,5-bis-trifluoromethyl-benzyloxy)-ethyl]-piperazin-1-yl}-acetic acid (compound 324; 0.75 g, 60%) as white needles.

[0130] Analysis for compound 324:

- $^1\text{H-NMR}$  (DMSO): 7.89 (s, 1H), 7.82 (s, 2H), 6.97 (t, 1H), 6.55-6.4 (m, 3H), 4.6 (dd, 2H), 3.85 (dd, 1H), 3.68 (dd, 1H), 3.52 (t, 1H), 3.34 (s, 2H), 3.2-3.0 (m, 4H), 2.8-2.5 (m, 4H).
- Mass : (LC/MS APCI+): 506 (MH+).

[0131] Another aspect of the invention concerns the use of a therapeutically effective amount of an  $\alpha$ -arylethylpiperazine derivative of formula I, an individual enantiomer, diastereoisomer or non-toxic pharmaceutically acceptable salt thereof for the prevention and/or treatment of a condition associated with pathological levels of substance P in a patient.

[0132] As used herein, "pathological levels of substance P" means a level of substance P sufficient to cause a pathological process leading to pain, emesis, pulmonary diseases such as asthma and bronchitis or allergic rhinitis. In a preferred embodiment, the present invention concerns the use of a therapeutically effective amount of an  $\alpha$ -arylethylpiperazine derivative of formula I, an individual enantiomer, diastereoisomer or non-toxic pharmaceutically acceptable salt thereof for the prevention and/or treatment of asthma and/or allergic rhinitis.

[0133] As used herein, "patient" means any living animal in need of prevention and/or treatment of symptoms associated with pathological levels of substance P. Such patients include most preferably humans.

[0134] As used herein, "a therapeutically effective amount" of an  $\alpha$ -arylethylpiperazine derivative of formula I an amount sufficient to at least ameliorate or prevent the symptoms of the patients. This amount may vary within wide limits depending on a series of factors such as the age and sex of the patient, the state of condition being treated, the overall health of the patient, the method of administration, the severity of side-effects and the like.

5 [0135] Preferably, the daily dosage is administered once or several times, depending on factors such as the severity of the condition, the mode of administration, the tolerance by the patient.

[0136] Accordingly, a further aspect of the invention concerns a pharmaceutical composition comprising a therapeutically effective amount of an  $\alpha$ -arylethylpiperazine derivative of formula I, an individual enantiomer, diastereoisomer or non-toxic pharmaceutically acceptable salt thereof, as well as pharmaceutically acceptable solid or liquid excipients or carriers therefor.

10 [0137] Suitable pharmaceutically acceptable excipient or carriers are the ones well known by the person skilled in the art and are prepared according to the methods generally applied by pharmacists, and may include solid, liquid or gaseous, non-toxic pharmaceutically acceptable vehicles. The percentage of active compound/pharmaceutically acceptable carrier may vary within very large ranges, only limited by the tolerance and the possible side-effects upon the patient. The limits are particularly determined by their frequency of administration.

15 [0138] For preparing solid compositions such as tablets, the compound according to the invention is mixed with conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gum. Solid formulations may also include sustained release excipients such as cellulose ester derivatives or any other known matricial excipient. Tablet formation by wet or dry granulation may take place 20 according to the methods well known by pharmacists.

[0139] Liquid formulations include syrups, aqueous or oil suspensions, flavoured emulsions... Compositions for inhalation include solutions and suspensions in pharmaceutically aqueous or organic solvents or powders, suitable for oral or nasal administration.

25 [0140] As indicated above, the  $\alpha$ -arylethylpiperazine derivatives of formula I, their individual enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof have the property of acting as neurokinin antagonists, without interacting with calcium channels. These advantageous properties are demonstrated by the following studies.

#### 1. Characterisation of the interactions between a test substance and the human recombinant NK<sub>1</sub> receptor.

30 [0141] Tachykinin receptors are divided into three subclasses : NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> receptors. NK<sub>1</sub> receptors are found on sensory nerve terminals, on smooth muscles and on immune cells. Their activation by substance P is involved in several pathophysiological states including, but not restricted to, asthma (mucus secretion, bronchoconstriction, plasma extravasation...), emesis and nociception (Bertrand and Geppetti, TIPS (1996), 17, 255-259; Longmore et al. DN&P (1995), 1, 1-23).

35 [0142] The recombinant human NK<sub>1</sub> receptor is coded by a gene located on chromosome 2 (Gerard N. et al., Biochemistry (1991), 30, 10640-10646.). Besides being more ethical, the use of human cloned receptors offers the advantage of population homogeneity (avoidance of cross binding of the test substances, including the radioligand, with other receptors or other receptor subtypes) and of being cloned from the target species i.e. human.

40 [0143] NK<sub>1</sub> receptors may be studied with [4,53H-Leu10] substance P, a commercially available radioligand. It offers a good selectivity, a high affinity and a low non specific binding (Aharony et al., The Journal of Pharmacology and Experimental Therapeutics (1991), 259, 146-155).

[0144] The following test was designed to assess the affinity of test substances for human recombinant NK<sub>1</sub> receptors expressed in Chinese Hamster Ovarian (CHO) cells.

#### 45 1.1. Cells.

[0145] CHO cells expressing the human recombinant NK<sub>1</sub> receptor are used. The cells were obtained from Euroscreen (Brussels, Belgium).

50 [0146] Cells expressing the human NK<sub>1</sub> receptor are routinely cultured in 175 cm<sup>2</sup> flasks containing 75 ml of medium F12 (Ham) enriched with 2 mmol/l L-glutamine, 100 IU/ml penicilline, 100  $\mu$ g/ml streptomycine, 1% sodium pyruvate, 2.5  $\mu$ g/ml fungizone amphotericin B, 400  $\mu$ g/ml geneticin and supplemented with 10 % foetal calf serum. The cells are grown at 37°C in a humidified atmosphere composed of 5% CO<sub>2</sub> and 95% air. When subcultured, the cells are seeded at a concentration of 50,000 cells/cm<sup>2</sup>.

## 1.2. Experimental procedure

## 1.2.1. Membrane preparation.

5 [0147] Confluent cells are gently scraped and resuspended in 25 ml of phosphate buffered saline without calcium and magnesium. The cellular suspension is centrifuged at 1500 x g for 3 min (4°C). The cell pellet is homogenized in a 15 mmol/l Tris-HCl (pH 7.5) buffer, 2 mmol/l MgCl<sub>2</sub>, 0.3 mmol/l EDTA, 1 mmol/l EGTA. The crude membrane fraction is collected by two consecutive centrifugation steps at 40,000 x g for 25 min (4°C). The final pellet is resuspended in 20 mmol/l Tris-HCl (pH 7.4), 250 mmol/l sucrose buffer at a protein concentration ranging from 2 to 6 mg/ml and stored in liquid nitrogen.

## 1.2.2. Test design.

15 [0148] The inhibition constant (Ki) is determined using increasing concentrations of the test substance. The concentration range usually encompasses 6 log units with variable steps (0.3 to 1 log). Assays are performed in mono- or duplicate.

20 [0149] Membranes are incubated at 25°C for 60 min in 0.5 ml of a 50 mmol/l Tris-HCl buffer (pH 7.4) containing 2 mmol/l MgCl<sub>2</sub>, 100 µg/ml bacitracine, 0.1 to 0.4 x 10<sup>-9</sup> mol/l of [4,5<sup>3</sup>H-Leu<sup>10</sup>] substance P (specific activity > 100 Ci/mmol) and increasing concentrations of the test substance. The non specific binding (NSB) is defined as the residual binding observed in the presence of a concentration in excess of reference substance (e.g. 10<sup>-6</sup> mol/l CP-96,345). Membrane-bound and free radioligands are separated by rapid filtration through glass fiber filters (equivalent to Whatman GF/C or GF/B; VEL, Belgium) presoaked in 0.1% polyethyleneimine to reduce non specific binding. Samples and filters are rinsed by at least 6 ml of 50 mmol/l Tris-HCl (pH 7.4) buffer. The entire filtration procedure does not exceed 10 seconds per sample. The radioactivity trapped onto the filters is counted by liquid scintillation in a β-counter (Tri-Carb 1900 or TopCount 9206, Cambera Packard, Belgium, or any other equivalent counter).

## 1.3. Data analysis.

30 [0150] Data analysis is performed by a computerized non linear (NLIN) curve fitting method using a set of equations describing several binding models assuming populations of independent non-interacting receptors which obey to the law of mass action (Weiland, G. A. and P. B. Molinoff, Life Science (1981), 29, 313-330 ; Molinoff P. et al., Life Science (1981), 29, 427-443). Initial values for the different variables may be provided by the experimenter.

## 1.4. Results.

35 [0151] Table A below summarizes the results obtained with the compounds according to the invention. In this Table, pIC<sub>50</sub> = - log IC<sub>50</sub>, IC<sub>50</sub> being the concentration of compound necessary to inhibit by 50% the specific binding of [4,5<sup>3</sup>H] substance P.

40

Table A

Binding of compounds of formula I to NK <sub>1</sub> receptors		
Cpd No.	Free base/Salt	pIC <sub>50</sub>
45	136	7.1
	138	8.0
	139	8.2
	141	8.1
	142	8.1
50	143	7.4
	144	7.4
	145	7.5
	146	7.8
	147	8.0
55	148	7.4
	149	7.2
	150	8.3

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Table A (continued)

Binding of compounds of formula I to NK <sub>1</sub> receptors			
	Cpd No.	Free base/Salt	pIC <sub>50</sub>
5	151	2 maleate	7.7
	152	2 maleate	7.9
	155	2 maleate	7.8
	156	2 maleate	8.1
10	157	2 HCl . 1/2 H <sub>2</sub> O	8.2
	158	2 maleate	8.1
	160	2 HCl	7.5
	161	3 HCl	8.1
	162	3 HCl	8.1
15	164	2 maleate	7.4
	170	3 HCl . 1/2 H <sub>2</sub> O	7.3
	171	-	7.1
	173	2 HCl	7.6
20	174	2 HCl	7.4
	175	2 HCl . 1 H <sub>2</sub> O	8.3
	176	2 HCl	7.6
	177	2 HCl	8.2
	182	2 maleate	7.0
25	191	2 HCl	7.2
	208	2 maleate	7.2
	219	2 maleate	9.5
	227	2 maleate	7.4
30	229	2 HCl	7.1
	230	2 HCl . 1/2 H <sub>2</sub> O	7.3
	231	2 HCl . 1 H <sub>2</sub> O	7.1
	232	2 maleate	7.3
	233	2 HCl	7.5
35	234	3/2 maleate	7.8
	235	2 maleate	7.2
	236	2 maleate	7.1
	237	2 maleate	7.0
40	239	2 HCl	7.5
	241	2 HCl . 1 H <sub>2</sub> O	8.1
	242	2 HCl . 1/2 H <sub>2</sub> O	8.1
	243	2 maleate . 1/2 H <sub>2</sub> O	7.2
	244	-	7.4
45	245	1 H <sub>2</sub> O	7.2
	246	2 maleate	7.1
	248	2 maleate	7.6
	249	2 maleate	7.5
50	250	2 HCl	7.1
	251	1 H <sub>2</sub> O	8.1
	252	1 H <sub>2</sub> O	7.7
	253	2 maleate	7.2
	254	1/2 H <sub>2</sub> O	7.3
55	255	2 HCl	7.1
	265	2 HCl	7.1
	269	2 maleate	7.0

Table A (continued)

Binding of compounds of formula I to NK <sub>1</sub> receptors			
	Cpd No.	Free base/Salt	pIC <sub>50</sub>
5	271	1 maleate . 1 H <sub>2</sub> O	7.4
	273	2 HCl . 3 H <sub>2</sub> O	8.5
	274	2 HCl . 1 H <sub>2</sub> O	7.9
	275	2 HCl . 5/2 H <sub>2</sub> O	8.4
10	277	2 HCl . 1 H <sub>2</sub> O	8.0
	279	2 HCl . 1 H <sub>2</sub> O	8.7
	281	2 HCl . 1/2 H <sub>2</sub> O	8.1
	283	2 HCl . 3/2 H <sub>2</sub> O	7.6
15	284	2 maleate . 1 H <sub>2</sub> O	7.3
	285	2 maleate . 1 H <sub>2</sub> O	7.3
	287	2 HCl . 1 H <sub>2</sub> O	7.5Cpd No.
	288	2 maleate . 1/2 H <sub>2</sub> O	8.3
	289	2 HCl	8.5
20	291	2 HCl	7.6
	292	2 maleate	7.8
	293	2 maleate	7.2
	294	2 maleate	7.9
	295	-	7.2
25	297	2 HCl	7.7
	298	2 HCl	7.8
	299	2 HCl	7.8
	300	2 HCl	7.5
30	301	2 HCl . 1/3 C <sub>3</sub> H <sub>8</sub> O	7.8
	302	2 HCl	8.4
	303	2 HCl	8.3
	304	2 maleate	8.1
	305	2 HCl . 3/2 H <sub>2</sub> O	7.1
35	306	1 H <sub>2</sub> O	7.5
	307	2 HCl	7.8
	308	2 HCl . 5/4 H <sub>2</sub> O	7.9
	312	2 HCl	7.6
	313	2 HCl	7.8
40	315	2 maleate . 1 H <sub>2</sub> O	8.3
	320	2 HCl	7.0

[0152] 2. Characterization of the interactions between a test substance and the verapamil binding site of the L-type calcium channel.

#### 2.1. Membrane preparation

[0153] 200-250 g male Sprague-Dawley rats are sacrificed by decapitation. Cerebral cortices are quickly dissected on ice and homogenized in a 20 mmol/l Tris-HCl (pH 7.4) buffer containing 250 mmol/l sucrose (buffer A). The homogenate is centrifuged at 30,000 g for 15 min at 4°C. The resulting crude membrane pellet is resuspended in a 50 mmol/l Tris-HCl (pH 7.4) buffer and incubated 15 min at 37°C before being centrifuged at 30,000 x g for 15 min at 4°C. After two more washes under the same conditions, the final pellet is resuspended in buffer A at a protein concentration ranging from 15 to 25 mg/ml and stored in liquid nitrogen.

#### 2.2. Binding experiments.

[0154] Binding experiments are essentially performed according to Reynolds J. et al., J. Pharmacol. Exp. Ther.

(1986), 237, 731-738. (1986) with slight modifications.

[0155] Membranes (120-175 µg/assay) are incubated at 25°C for 60 min in 0.5 ml of a 50 mmol/l Tris-HCl buffer (pH 7.4) containing 2 mmol/l MgCl<sub>2</sub>, 0.2 to 0.4 x 10<sup>-9</sup> mol/l of [<sup>3</sup>H]D888 (85 Ci/mmol; Amersham, Belgium) and 10 µmol/l of the test substance. The non specific binding (NSB) is defined as the residual binding observed in the presence 10 µM verapamil. Membrane-bound and -free radioligands are separated by rapid filtration through glass fiber filters (equivalent to Whatman GF/C or GF/B; VEL, Belgium) presoaked in 0.1% polyethyleneimine to reduce non specific binding. Samples and filters are rinsed by at least 6 ml of 50 mmol/l Tris-HCl (pH 7.4) buffer. The entire filtration procedure does not exceed 10 seconds per sample. The radioactivity trapped onto the filters is counted by liquid scintillation in a β-counter.

### 10 2.3. Data analysis.

[0156] The inhibition of the radioligand specific binding is calculated as follows:

$$15 \quad \% \text{ inhibition} = 100 - \left( \frac{B_I - B_{NS}}{B_O - B_{NS}} \times 100 \right)$$

where:

- 20 - B<sub>I</sub> and B<sub>O</sub> represent the binding observed in the presence and absence of the test substance respectively; and
- B<sub>NS</sub> is the non specific binding.

[0157] Data analysis is performed by a computerized non linear curve fitting method using a set of equations describing several binding models assuming competitive interactions between ligands (Weiland G.A. and P.B. Molinoff Life Science (1981), 29, 313-330; Molinoff P. et al. (1981) Life Sci., 29, 427-443).

### 25 2.4. Results.

30 [0158] Table B below summarizes the results obtained with the compounds according to the invention.

Table B -

Inhibition of [ <sup>3</sup> H]D888 binding to the verapamil binding site of the L-type calcium channel by 10 µmol/l of test substances.		
Cpd No.	Free base/Salt	% inhibition*
160	2 HCl	0
229	2 HCl	0
230	2 HCl . 1/2 H <sub>2</sub> O	0
231	2 HCl, 1 H <sub>2</sub> O	0
232	2 maleate	+
233	2 HCl	0
234	3/2 maleate	0
235	2 maleate	0
236	2 maleate	0
237	2 maleate	0
239	2 HCl	0
241	2 HCl . 1 H <sub>2</sub> O	+
242	2 HCl . 1/2 H <sub>2</sub> O	+
243	2 maleate . 1/2 H <sub>2</sub> O	0
244	- +	
245	1 H <sub>2</sub> O	0

\*0 : inhibition < 20%; + : inhibition comprised between 20 and 50%.

Cpd = compound.

Table B - (continued)

Inhibition of [<sup>3</sup>H]D888 binding to the verapamil binding site of the L-type calcium channel by 10 µmol/l of test substances.

Cpd No.	Free base/Salt	% inhibition*
246	2 maleate	+
248	2 maleate	+
249	2 maleate	+
250	2 HCl	+
251	1 H <sub>2</sub> O	+
252	1 H <sub>2</sub> O	+
253	2 maleate	0
254	1/2 H <sub>2</sub> O	0
255	2 HCl	0
265	2 HCl	0
269	2 maleate	0
271	1 maleate . 1 H <sub>2</sub> O	+
273	2 HCl . 3 H <sub>2</sub> O	0
274	2 HCl . 1 H <sub>2</sub> O	0
275	2 HCl . 5/2 H <sub>2</sub> O	0
277	2 HCl . 1 H <sub>2</sub> O	0
279	2 HCl . 1 H <sub>2</sub> O	0
281	2 HCl . 1/2 H <sub>2</sub> O	+
283	2 HCl . 3/2 H <sub>2</sub> O	+
285	2 maleate . 1 H <sub>2</sub> O	+
287	2 HCl . 1 H <sub>2</sub> O	+
291	2 HCl	0
292	2 maleate	+
295	- +	
297	2 HCl	+
298	2 HCl	+
299	2 HCl	+
300	2 HCl	+
301	2 HCl . 1/3 C <sub>3</sub> H <sub>8</sub> O	+
302	2 HCl	+
303	2 HCl	+
304	2 maleate	+
305	2 HCl . 3/2 H <sub>2</sub> O	0
306	1 H <sub>2</sub> O	+
307	2 HCl	+
312	2 HCl	0
313	2 HCl	0
320	2 HCl	0

\*0 : inhibition < 20%; + : inhibition comprised between 20 and 50%.

Cpd = compound.

### 3. Effect of compound on isolated rat aorta contracted by 100 mM KCl.

[0159] Rat thoracic aorta depolarized by 100 mM KCl develops a contraction induced by an influx of Ca<sup>2+</sup> into the smooth muscle cell. An inhibition of this contraction could predict a Ca<sup>2+</sup> antagonist activity.

[0160] The method was adapted from Polster P. et al., J. Pharmacol. Exp. Ther. (1990), 255, 593: rings of thoracic

aorta were prepared from male Wistar rats (250 - 400 g) and mounted under an optimal resting tension of 2 g in 10 ml organ baths containing modified Krebs' solution (NaCl 112 mM, NaHCO<sub>3</sub> 25 mM, KCl 5 mM, MgSO<sub>4</sub> 1.2 mM, CaCl<sub>2</sub> 2.5 mM, KH<sub>2</sub>PO<sub>4</sub> 1 mM and glucose 11.5 mM, pH 7.4). The bathing solution was maintained at a temperature of 37°C and gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. Isometric contractions were measured with a force transducer connected to an amplifier. A computer system was used to control data acquisition and fluid circulation through electrovalves. Drugs were manually injected into the bath.

[0161] Each ring was allowed to equilibrate for 60 min in the modified Krebs' solution. Control contractions were repeatedly induced by a depolarising medium (NaCl 17 mM, NaHCO<sub>3</sub> 25 mM, KCl 100 mM, MgSO<sub>4</sub> 1.2 mM, CaCl<sub>2</sub> 2.5 mM, KH<sub>2</sub>PO<sub>4</sub> 1.2 mM et glucose 11.5 mM, pH 7.4). After obtaining two reproducible control contractions, a 3rd contraction was induced and the test compound was added to the bathing medium for 2 hours. Only preparation in which the contractions were matched were used. Each tissue received only one concentration of the test compound. Appropriate control experiments were conducted in order to test the effect of the solvent.

[0162] To normalize data, the change in tension due to the drug was compared to the change of tension due to the solvant and expressed as percentage of the induced relaxation of the initial contraction. Raw data were processed by a computer system and the pD'2 value was calculated following the method of Van Rossum J.M. et al., Arch. Int. Pharmacodyn. Ther. (1963), 143, 299.

[0163] Table C below summarizes the results obtained with the compounds according to the invention. This table shows that none of the tested compounds inhibited the contraction induced by 100 mM KCl on isolated rat aorta. These results suggest that a Ca<sup>2+</sup> antagonist activity is not to be taking into account for these compounds.

Table C -

Effect of compound on isolated rat aorta contracted by 100 mM KCl			
	Cpd No.	Free base/Salt	Result
25	160	2 HCl	inactive à 10 <sup>-5</sup> M
	229	2 HCl	inactive à 10 <sup>-5</sup> M
	230	2 HCl . 1/2 H <sub>2</sub> O	inactive à 10 <sup>-5</sup> M
	232	2 maleate	inactive à 10 <sup>-5</sup> M
30	233	2 HCl	inactive à 10 <sup>-5</sup> M
	235	2 maleate	inactive à 10 <sup>-5</sup> M
	236	2 maleate	inactive à 10 <sup>-5</sup> M
	237	2 maleate	inactive à 10 <sup>-5</sup> M
35	242	2 HCl . 1/2 H <sub>2</sub> O	inactive à 10 <sup>-5</sup> M
	243	2 maleate . 1/2 H <sub>2</sub> O	inactive à 10 <sup>-5</sup> M
	265	2 HCl	inactive à 10 <sup>-5</sup> M
	281	2 HCl . 1/2 H <sub>2</sub> O	inactive à 10 <sup>-5</sup> M
	287	2 HCl . 1 H <sub>2</sub> O	inactive à 10 <sup>-5</sup> M
40	295	-	inactive à 10 <sup>-5</sup> M
	297	2 HCl	inactive à 10 <sup>-5</sup> M
	298	2 HCl	inactive à 10 <sup>-5</sup> M
	299	2 HCl	inactive à 10 <sup>-5</sup> M
45	300	2 HCl	inactive à 10 <sup>-5</sup> M
	301	2 HCl . 1/3 C <sub>3</sub> H <sub>8</sub> O	inactive à 10 <sup>-5</sup> M
	303	2 HCl	inactive à 10 <sup>-5</sup> M
	304	2 maleate	inactive à 10 <sup>-5</sup> M
	312	2 HCl	inactive à 10 <sup>-5</sup> M

50 4. Effect of compound on isolated guinea pig ileum contracted by substance P.

[0164] Measuring the effect of compounds in isolated guinea pig ileum stimulated by substance P is a functional test relevant to determine potency of the compounds and nature of the NK<sub>1</sub> antagonism. The method was adapted from Meini S. et al., Neuropeptides (1995), 28, 99: segments of ileum were prepared from male Dunkin-Hartley guinea pig (300 - 600 g) and mounted under an optimal resting tension of 0.5 g in 10 ml organ baths containing modified Tyrode solution (NaCl 136.9 mM, NaHCO<sub>3</sub> 11.9 mM, KCl 2.7 mM, MgCl<sub>2</sub> 1.05 mM, CaCl<sub>2</sub> 1.8 mM, NaH<sub>2</sub>PO<sub>4</sub> 0.42 mM and glucose 5.6 mM, atropine 5 µM, indomethacine 3 µM and chlorpheniramine 1 µM, pH 6.8). The bathing solution was

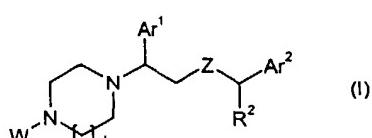
maintained at a temperature of 37°C and gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. Isometric contractions were measured with a force transducer connected to an amplifier. A computer system was used to control data acquisition and fluid circulation through electrovalves. Drugs were manually injected into the bath.

[0165] Each segment was allowed to equilibrate for 60 min in the modified Tyrode solution. Control contractions were repeatedly induced by a 30 nM substance P. After obtaining reproducible control contractions, six cumulative concentration-response curves to substance P (0.01 nM to 1 μM) were constructed in the absence or presence of the test compound (incubation time : 30 min). Only preparation in which the control contractions were matched were used. Each tissue received four concentrations of the test compound. Appropriate control experiments were conducted in order to test the effect of the solvent.

[0166] Raw data were processed by a computer system and the pD<sub>2</sub>, pD'<sub>2</sub> and/or pA<sub>2</sub> values were calculated following the method of Van Rossum J.M. et al., Arch. Int. Pharmacodyn. Ther. (1963), 143, 299 or Arunlakshana O. and Schild H.O., Br. J. Pharmacol. (1959), 14, 48.

## Claims

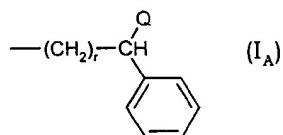
### 1. α-arylethylpiperazine derivatives of formula I



wherein

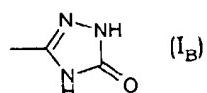
- Z represents O or S;
- n' represents 1 or 2;
- R<sup>2</sup> represents a hydrogen atom or a methyl group;
- W represents

(i) a cyclohexyl group substituted by a COOH, 2-phenylacetic acid or alkyl 2-phenylacetate group,  
 (ii) a group of formula



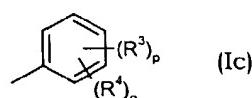
wherein r represents 1, 2 or 3 and Q represents OH or -NH-CO-CH<sub>3</sub>, or  
 (iii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which

- R<sup>1</sup> represents a CN, CONR<sup>i</sup>R<sup>ii</sup>, CONHOH, CONHCH<sub>2</sub>CO<sub>2</sub>H, CONHCH<sub>2</sub>CO<sub>2</sub>alkyl, CONHSO<sub>2</sub>alkyl, CONHSO<sub>2</sub>phenyl, CONHSO<sub>2</sub>toly, COOH, COOalkyl, OH, SO<sub>3</sub>H, PO(OR<sup>iii</sup>)(OR<sup>iv</sup>) group, a mono-, di- or tri-substituted phenyl group in which the substituent is selected from COOH, COOalkyl or OCH<sub>3</sub>, a heteroaryl, a tetrazole, a morpholine, a thiomorpholine, a thiomorpholine S,S-dioxide, a phthalimide group or a triazolone of formula



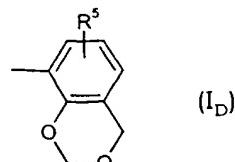
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- 5 wherein R<sup>i</sup>, R<sup>ii</sup>, R<sup>iii</sup> and R<sup>iv</sup> independently represent a hydrogen atom or an alkyl group;
- X represents a single bond, an oxygen atom or a methylene group;
  - m represents 1 or 2, provided that m is not 1 when X is O;
  - n represents 0, 1 or 2, provided that N is not 0 or 1 when X represents O and R<sup>1</sup> represents OH;
- 10 - Ar<sup>1</sup> represents a phenyl, aryl, heteroaryl, or mono-, di- or tri-substituted phenyl group in which the substituents are selected from a halogen atom, an alkyl, trifluoromethyl, hydroxy, alkoxy, SCH<sub>3</sub>, CN, NO<sub>2</sub>, CONH<sub>2</sub>, COOH, COOalkyl or amino group, or mono-substituted heteroaryl group in which substituent is a halogen atom;
- 15 - Ar<sup>2</sup> represents a substituted phenyl group of formula



in which

- 20 - R<sup>3</sup> represents a halogen atom, an alkyl, alkoxy, trifluoromethyl, COOH, CN, COOalkyl or CONH<sub>2</sub> group;
- R<sup>4</sup> represents a halogen atom, a trifluoromethyl or alkyl group;
  - p and q independently represent 0, 1, 2 or 3; or a group of formula

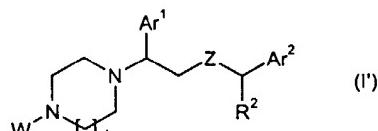


30 in which R<sup>5</sup> represents a halogen atom;

all alkyl and alkoxy groups being linear or branched and having from 1 to 4 atoms of carbon,

35 as well as non-toxic pharmaceutically acceptable salts, individual optical isomers, individual diastereoisomers or prodrugs thereof.

2. α-arylethylpiperazine according to claim 1, characterized in that it is a compound of formula I'

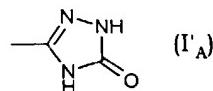


45 wherein

- Z represents an oxygen atom;
- n' represents 1;
- R<sup>2</sup> represents a hydrogen atom or a methyl group;
- W represents

50 (i) a cyclohexyl group substituted by a COOH, or  
(ii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which

- 55 - R<sup>1</sup> represents a CN, CONHSO<sub>2</sub>alkyl, COOH, COOalkyl, SO<sub>3</sub>H, PO(OH)<sub>2</sub>, a phenyl group mono-substituted by COOH, a tetrazole group or a triazolone of formula



- 5
- X represents a single bond, an oxygen atom or a methylene group;
  - m represents 1 or 2, provided that m is not 1 when X is an oxygen atom;
  - n represents 0, 1 or 2, provided that n is not 0 or 1 when X represents an oxygen atom and R<sup>1</sup> represents OH;
- 10
- Ar<sup>1</sup> represents phenyl, a mono-, di- or tri-substituted phenyl group in which the substituents are selected from a halogen atom, an alkyl group, CN or NO<sub>2</sub>;
  - Ar<sup>2</sup> represents a substituted aryl group of formula



- 20
- in which
- R<sup>3</sup> represents a halogen atom or a trifluoromethyl group;
  - p represents 0, 1, 2 or 3;
- 25
- the alkyl groups being linear or branched and having 1 to 4 atoms of carbon, as well as non-toxic pharmaceutically acceptable salts, individual optical isomers, individual diastereoisomers or prodrugs thereof.

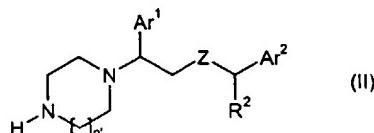
3. α-arylethylpiperazine derivative according to claim 1 or 2 characterized in that it is selected from the group consisting of:

- 30
- [2-[2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl]-piperazin-1-yl]-ethoxy]-acetic acid;
  - (4-[2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl]-piperazin-1-yl)-acetic acid;
  - 4-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-yl]-cyclohexanecarboxylic acid;
  - 6-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-yl]-hexanoic acid;
- 35
- {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl}-piperazin-1-yl]-acetonitrile;
  - 3-{4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl}-piperazin-1-yl]-propane-1-sulfonic acid;
  - 5-{4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl}-piperazin-1-yl]-pentanoic acid;
  - (2-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-yl]-ethoxy)-acetic acid;
- 40
- {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl}-piperazin-1-yl]-acetic acid;
  - {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-(3,4,5-trifluoro-phenyl)-ethyl}-piperazin-1-yl]-acetic acid;
  - 4-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-ylmethyl]-benzoic acid;
  - (4-[2-(3,5-Dibromo-benzyl)oxy]-1-phenyl-ethyl)-piperazin-1-yl]-acetic acid;
- 45
- {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-para-tolyl-ethyl}-piperazin-1-yl]-acetic acid;
  - (2-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-yl]-ethyl)-phosphonic acid;
  - {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-(2,3-difluoro-phenyl)-ethyl}-piperazin-1-yl]-acetic acid;
  - {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-(2-nitro-phenyl)-ethyl}-piperazin-1-yl]-acetic acid;
- 50
- N-[{(2-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-yl)-ethoxy}-acetyl]-methanesulfonamide;
  - {4-[2-(3,5-Dichloro-benzyl)oxy]-1-phenyl-ethyl}-piperazin-1-yl]-acetic acid;
  - {4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-(4-cyano-phenyl)-ethyl}-piperazin-1-yl]-acetic acid;
  - 5-{4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl}-piperazin-1-ylmethyl]-2,4-dihydro-[1,2,4]triazol-3-one;
  - 1-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine;
- 55
- 1-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-4-[2-(1H-tetrazol-5-ylmethoxy)-ethyl]-piperazine;
  - 1-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-(4-fluoro-phenyl)-ethyl]-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine;
  - 1-{2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl}-4-[4-(1H-tetrazol-5-yl)-butyl]-piperazine;
  - 1-{2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-1-phenyl-ethyl}-4-[5-(1H-tetrazol-5-yl)-pentyl]-piperazine;
  - (2-[4-[2-(3,5-Bis-trifluoromethyl-benzyl)oxy]-1-phenyl-ethyl]-piperazin-1-yl)-ethoxy]-acetic acid isobutyl ester;

- 3-{4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-ylmethyl}-benzoic acid;  
 - 4-(4-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-1-phenyl-ethyl]-piperazin-1-yl)-butyric acid;

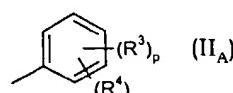
as well as non-toxic pharmaceutically acceptable salts, individual optical isomers or individual diastereoisomers thereof.

4.  $\alpha$ -arylethylpiperazine derivative of formula II



15 wherein

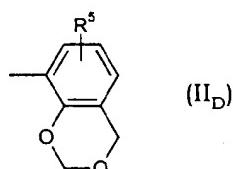
- Z represents O or S;
- n' represents 1 or 2;
- R<sup>2</sup> represents a hydrogen atom or a methyl group;
- Ar<sup>1</sup> represents a phenyl, aryl, heteroaryl, or mono-, di- or tri-substituted phenyl group in which the substituents are selected from a halogen atom, an alkyl, trifluoromethyl, hydroxy, alkoxy, SCH<sub>3</sub>, CN, NO<sub>2</sub>, CONH<sub>2</sub>, COOH, COOalkyl or amino group, or mono-substituted heteroaryl group in which substituent is a halogen atom;
- Ar<sup>2</sup> represents a substituted phenyl group of formula



25 in which

- R<sup>3</sup> represents a halogen atom, an alkyl, alkoxy, trifluoromethyl, COOH, CN, COOalkyl or CONH<sub>2</sub> group;
- R<sup>4</sup> represents a halogen atom, a trifluoromethyl or alkyl group;
- p and q independently represent 0, 1, 2 or 3, provided that p is not 0 and q is not 0 when Ar<sup>1</sup> is a phenyl para-substituted by a Fluorine atom;

30 or a group of formula



40 in which R<sup>5</sup> represents a halogen atom;

45 as well as non-toxic pharmaceutically acceptable salts, individual optical isomers or individual diastereoisomers thereof.

50 5. A process for the preparation of an  $\alpha$ -arylethylpiperazine derivative according to claim 1, characterized in that it comprises the steps of

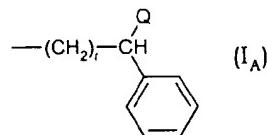
- 55 (a) when, in formula I, Ar<sup>1</sup> represents a phenyl, aryl or heteroaryl group, a mono-, di- or trisubstituted phenyl group in which the substituents are selected from a halogen atom, an alkyl, trifluoromethyl, alkoxy, SCH<sub>3</sub> or NO<sub>2</sub> group, or a mono-substituted heteroaryl group in which substituent is a halogen atom, Ar<sup>2</sup>, Z, R<sup>2</sup> and n'

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having the same meanings as given above in general formula I, and, furthermore,

(a.1) when, in formula I, W represents

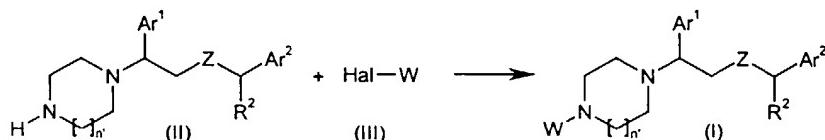
- 5 (i) an alkyl 2-phenylacetate group,  
(ii) a group of formula



15 wherein r represents 1, 2 or 3 and Q represents OH, or  
(iii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which

20 R<sup>1</sup> represents a CN, CONR<sup>i</sup>R<sup>ii</sup>, COOalkyl, OH, SO<sub>3</sub>H or PO(OR<sup>iii</sup>)(OR<sup>iv</sup>) group, a mono-, di- or tri-substituted phenyl group in which the substituent is COOalkyl or OCH<sub>3</sub>, a pyridine, morpholine, thiomorpholine, thiomorpholine-(S,S)-dioxide or phthalimide group, wherein R<sup>i</sup> and R<sup>ii</sup> represent a hydrogen atom or an alkyl group and R<sup>iii</sup> and R<sup>iv</sup> represent an alkyl group,  
n, m and X having the same meanings as given above in general formula I,

25 an  $\alpha$ -arylethylpiperazine of formula II is reacted with a compound of formula III according to the equation



35 wherein Ar<sup>1</sup>, Ar<sup>2</sup>, Z, R<sup>2</sup>, n' and W have the same meanings as stated above and Hal represents a halogen atom, preferably a chlorine, bromine or iodine atom; or

(a.2) when, in formula I, W represents

- 40 (i) 2-phenylacetic acid, or  
(ii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>-, in which

45 R<sup>1</sup> represents CONHCH<sub>2</sub>CO<sub>2</sub>H, COOH, PO(OH)(OEt), PO(OH)<sub>2</sub> or a mono-, di- or trisubstituted phenyl group in which the substituents are COOH,  
n, m and X having the same meanings as given above in general formula I,

45 the corresponding compound of formula I wherein W is

- 50 (i) an alkyl 2-phenylacetate or  
(ii) a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- in which R<sup>1</sup> represents CN, CONH<sub>2</sub>, CONHCH<sub>2</sub>CO<sub>2</sub>alkyl, COOalkyl, PO(OEt)<sub>2</sub> or a mono-, di- or tri-substituted phenyl group in which the substituent is COOalkyl, n, m and X having the same meanings as given above in general formula I,

55 is hydrolysed in an aqueous, alcoholic or aqueous-alcoholic medium by an acid or a base; or  
(a.3) when, in formula I, W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- wherein n, m and X have the same meaning as given above in general formula I, and

- a.3.1. R<sup>1</sup> is CN, the corresponding compound of formula I in which R<sup>1</sup> is CONH<sub>2</sub> is dehydrated;  
a.3.2. R<sup>1</sup> is CONH<sub>2</sub>, the corresponding compound of formula I in which R<sup>1</sup> is COOalkyl is ammon-

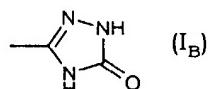
olyzed;

a.3.3. R<sup>1</sup> is COOalkyl or CONHCH<sub>2</sub>COOalkyl, the corresponding compound of formula I in which R<sup>1</sup> is COOH or CONHCH<sub>2</sub>COOH is esterified;

a.3.4. R<sup>1</sup> is CONR<sup>i</sup>R<sup>ii</sup>, R<sup>i</sup> and R<sup>ii</sup> independently representing a hydrogen atom or an alkyl group, at least one of R<sup>i</sup> or R<sup>ii</sup> being an alkyl group, the corresponding compound of formula I in which R<sup>1</sup> is COOH or COOalkyl is aminolyzed; or

(a.4) when, in formula I, W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- wherein R<sup>1</sup> represents a triazolone of formula

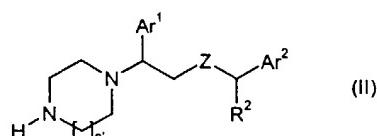
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and n, m and X have the same meanings as in general formula I, an  $\alpha$ -arylethylpiperazine of formula II

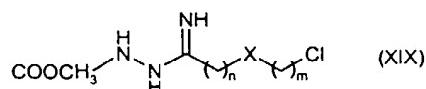
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wherein Ar<sup>1</sup>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as stated above is reacted with a (chloromethyl) amidrazone of formula XIX.

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wherein n, m and X have the same meanings as stated above; or

(a.5) when, in formula I, W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- wherein R<sup>1</sup> is a tetrazole, n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I wherein R<sup>1</sup> is CN is reacted with azidotrimethylsilane in the presence of dibutyltin oxide; or

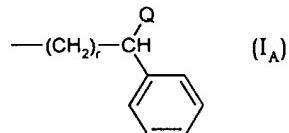
(a.6) when, in formula I, W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>- wherein R<sup>1</sup> represents CONHSO<sub>2</sub>alkyl, CONHSO<sub>2</sub>phenyl or CONHSO<sub>2</sub>tolyl, n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I in which R<sup>1</sup> is COOH is reacted with a sulfonamide of formula R<sup>v</sup>-SO<sub>2</sub>-NH<sub>2</sub> in which R<sup>v</sup> represents an alkyl, phenyl or 4-methylphenyl group; or

(a.7) when, in formula I, W is a group of formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>n</sub>-X-(CH<sub>2</sub>)<sub>m</sub>, wherein R<sup>1</sup> represents CONHSO<sub>2</sub>alkyl, CONHSO<sub>2</sub>phenyl or CONHSO<sub>2</sub>tolyl, n=0, X=O and m=2, the corresponding  $\alpha$ -arylethylpiperazine of formula I wherein R<sup>1</sup> is HO-(CH<sub>2</sub>)<sub>m</sub> is reacted with the compound of formula R-SO<sub>2</sub>-N=C=O in which R represents alkyl, phenyl or 4-methylphenyl; or

(a.8) when, in formula I, W is a group of formula

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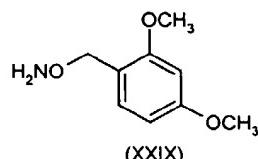
wherein Q=NH(CO)CH<sub>3</sub>, the corresponding compound of formula I in which Q is OH is reacted with acetonitrile in the presence of acid; or

(a.9) when, in formula I, W is a cyclohexyl group substituted by COOH, the corresponding compound of formula I in which W is a cyclohexyl group substituted by COOalkyl is hydrolysed in an aqueous, alcoholic

or aqueous-alcoholic medium in presence of an acid or a base; or  
 (a. 10) when, in formula I, W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m$  wherein  $R^1$  represents CONHOH, n, m and X having the same meanings as given above in general formula I, a corresponding compound of formula I wherein  $R^1$  represents COOH is coupled with the compound of formula XXIX

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followed by treatment with trifluoroacetic acid; or

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- (b) when, in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOCH<sub>3</sub>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I and W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m$  wherein R<sup>1</sup> represents COOalkyl, n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are bromine atoms is submitted to methoxycarbonylation by carbon monoxide treatment in the presence of palladium(II) acetate, 1,3-bis(diphenylphosphino)propane and triethylamine; or
- (c) when, in formula I, Ar<sup>1</sup> is mono-, di- or tri-substituted phenyl group in which the substituents are CN, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I and W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m$  wherein R<sup>1</sup> represents COOalkyl, n, m and X having the same meanings as in general formula I, a corresponding compound of formula I Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are Bromine atoms is reacted with zinc cyanide; or
- (d) when in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOH or CONH<sub>2</sub>, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOalkyl is hydrolysed or ammonolyzed; optionally, this transformation may take place simultaneously with hydrolysis or ammonolysis of another COOalkyl group of the compound of formula I;
- (e) when in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are COOH, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are by CN is hydrolysed; optionally, this transformation may take place simultaneously with the hydrolysis of another CN group of the compound of formula I; or
- (f) when in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are CN, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' have the same meanings as given above in general formula I and W is a group of formula  $R^1-(CH_2)_n-X-(CH_2)_m$  wherein R<sup>1</sup> represents COOH and n, m and X have the same meaning as stated above for general formula I, the corresponding compound of formula I in which R<sup>1</sup> is COOalkyl is hydrolysed; or
- (g) when, in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are NH<sub>2</sub> and W is a group of formula  $R_1-(CH_2)_n-X-(CH_2)_m$  wherein R<sup>1</sup> represents COOH or COOalkyl, Ar<sup>2</sup>, Z, R<sup>2</sup>, n', n, m and X having the same meanings as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are NO<sub>2</sub> is reduced; or
- (h) when, in formula I, Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are OH, W, Ar<sup>2</sup>, Z, R<sup>2</sup> and n' having the same meaning as given above in general formula I, the corresponding compound of formula I in which Ar<sup>1</sup> is a mono-, di- or tri-substituted phenyl group in which the substituents are OP', wherein P' is a protecting group, is deprotected; and
- (i) optionally, the  $\alpha$ -arylethylpiperazine derivative of formula I so-obtained is converted into one of its non-toxic pharmaceutically acceptable salts.

6. A process according to claim 5, characterized in that the compound of formula I is further resolved into its individual optical isomers.
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7. Use of a therapeutically effective amount of an  $\alpha$ -arylethylpiperazine derivative according to claims 1 to 4, an individual enantiomer, diastereoisomer or non-toxic pharmaceutically acceptable salt thereof for the prevention and/or treatment of a condition associated with pathological levels of substance P in a patient.

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8. Use according to claim 7, characterized in that a therapeutically effective amount of an  $\alpha$ -arylethylpiperazine derivative of formula I, an individual enantiomer, diastereoisomer or non-toxic pharmaceutically acceptable salt thereof allows the prevention and/or treatment of asthma and/or allergic rhinitis.
- 5      9. A pharmaceutical composition comprising a therapeutically effective amount of an  $\alpha$ -arylethylpiperazine derivative according to claims 1 to 4, an individual enantiomer, diastereoisomer or non-toxic pharmaceutically acceptable salt thereof, as well as pharmaceutically acceptable solid or liquid excipients or carriers therefor.

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## PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 99 12 5359 shall be considered, for the purposes of subsequent proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D,A	DE 195 20 499 A (BOEHRINGER INGELHEIM) 21 March 1996 (1996-03-21) * claims; examples * -----	1,7,9	C07D295/088 C07D295/13 C07D295/15 A61K31/495
A	WO 96 32386 A (BOEHRINGER INGELHEIM) 17 October 1996 (1996-10-17) * claims; examples 1,3-6,18,21-33,39-42,52-68 *	1,7,9	A61P11/06 C07D213/36 C07D209/48 C07F9/6509
D,A	WO 94 14767 A (MERCK SHARP & DOHME) 7 July 1994 (1994-07-07) * page 6, line 6 - page 7, line 10 * * page 10, line 25 - page 12, line 6; claims; examples * -----	1,7,9	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D C07F A61K A61P
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>Although claims 7 - 8 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compounds.</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	15 May 2000	ZERVAS, B	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 12 5359

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-05-2000

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
DE 19520499	A	21-03-1996		AU 3567195 A CA 2200083 A WO 9608480 A EP 0781277 A JP 10505826 T TR 960229 A US 5696123 A US 5985881 A US 5708006 A	29-03-1996 21-03-1996 21-03-1996 02-07-1997 09-06-1998 21-06-1996 09-12-1997 16-11-1999 13-01-1998
WO 9632386	A	17-10-1996		DE 19519245 A AU 706209 B AU 5687496 A BG 62138 B BG 101947 A BR 9604821 A CA 2218096 A CZ 9703257 A EP 0824530 A HR 960168 A HU 9802270 A JP 11503441 T NO 974734 A PL 322768 A SK 138797 A US 5710155 A US 5861509 A ZA 9602916 A	17-10-1996 10-06-1999 30-10-1996 31-03-1999 29-05-1998 09-06-1998 17-10-1996 17-06-1998 25-02-1998 31-08-1997 28-09-1999 26-03-1999 13-10-1997 16-02-1998 04-03-1998 20-01-1998 19-01-1999 14-10-1996
WO 9414767	A	07-07-1994		AU 5704894 A US 5624947 A	19-07-1994 29-04-1997